(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 September 2002 (06.09.2002)

PCT

(10) International Publication Number
WO 02/067654 A2

(51) International Patent Classification: Not classified

(21) International Application Number: PCT/US02/06002

(22) International Filing Date: 27 February 2002 (27.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/794,825 27 February 2001 (27.02.2001) US

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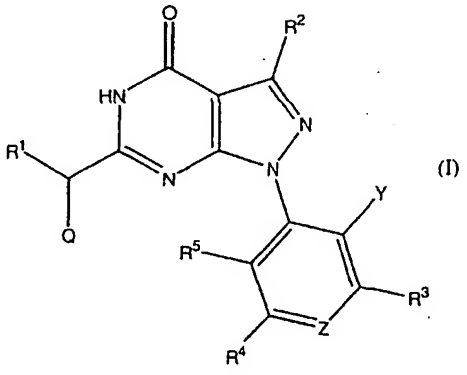
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

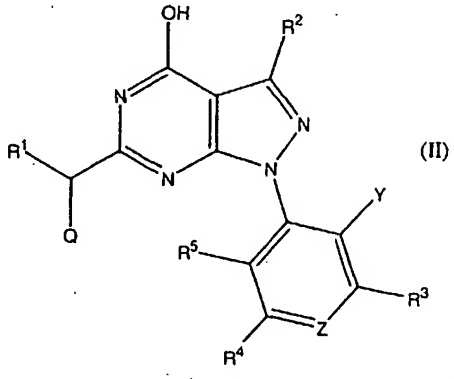
Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 6-SUBSTITUTED PYRAZOLO[3,4-D]PYRIMIDIN-4-ONES USEFUL AS CYCLIN DEPENDENT KINASE INHIBITORS



(I)



(II)

(57) Abstract: The present invention relates to the synthesis of a novel class of pyrazolo[3,4-d]pyrimidin-4-ones of formula (I), alternatively represented by the tautomer (II), that are potent inhibitors of the class of enzymes known as cyclin dependent kinases, which relate to the catalytic subunits cyclin dependent kinase 1-8 and their regulatory subunits know as cyclins A-H, K, N, and T. This invention also provides a novel method of treating cancer or other proliferative diseases by administering a therapeutically effective amount of one of these compounds or a pharmaceutically acceptable salt form thereof. Alternatively, one can treat cancer or other proliferative diseases by administering a therapeutically effective combination of one of the compounds of the present invention and one or more other known anti-cancer or anti-proliferative agents.

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TITLE

6-Substituted pyrazolo[3,4-d]pyrimidin-4-ones Useful as Cyclin Dependent Kinase Inhibitors

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority from U.S. Serial No. 09/794,825 filed February 27, 2001 in the name of Markwalder et al., the disclosure of which is herein incorporated by reference as though set forth in full.

FIELD OF THE INVENTION

This invention relates to 6-substituted pyrazolo[3,4-d]pyrimidin-4-ones useful as cyclin dependent kinase (cdk) inhibitors, pharmaceutical compositions comprising the same, methods for using these compounds for treating cancer and proliferative diseases, and intermediates and processes for making the same.

BACKGROUND OF THE INVENTION

One of the most important and fundamental processes in biology is the division of cells mediated by the cell cycle. This process ensures the controlled production of subsequent generations of cells with defined biological function. It is a highly regulated phenomenon and responds to a diverse set of cellular signals both within the cell and from external sources. A complex network of tumor promoting and suppressing gene products are key components of this cellular signaling process. Overexpression of the tumor promoting components or the subsequent loss of the tumor suppressing products will lead to unregulated cellular proliferation and the generation of tumors (Pardee, *Science* 246:603-608, 1989).

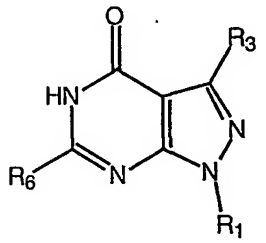
Cyclin dependent kinases play a key role in regulating the cell cycle machinery. These complexes consist of two components: a catalytic subunit (the kinase) and a regulatory subunit (the cyclin). To date,

eight kinase subunits (cyclin dependent kinase 1-8) have been identified along with several regulatory subunits (cyclins A-H, K, N, and T). Each kinase associates with a specific regulatory partner and together make up the active catalytic moiety. Each transition of the cell cycle is regulated by a particular cyclin dependent kinase complex: G1/S by cyclin dependent kinase2/cyclin E, cyclin dependent kinase4/cyclin D1 and cyclin dependent kinase6/cyclinD2; S/G2 by cyclin dependent kinase2/cyclin A and cyclin dependent kinase1/cyclin A; G2/M by cyclin dependent kinase1/cyclinB. The coordinated activity of these kinases guides the individual cells through the replication process and ensures the vitality of each subsequent generation (Sherr, *Cell* 73:1059-1065, 1993; Draetta, *Trends Biochem. Sci.* 15:378-382, 1990).

An increasing body of evidence has shown a link between tumor development and cyclin dependent kinase related malfunctions. Over expression of the cyclin regulatory proteins and subsequent kinase hyperactivity have been linked to several types of cancers (Jiang, *Proc. Natl. Acad. Sci. USA* 90:9026-9030, 1993; Wang, *Nature* 343:555-557, 1990). More recently, endogenous, highly specific protein inhibitors of cyclin dependent kinases were found to have a major affect on cellular proliferation (Kamb et al., *Science* 264:436-440, 1994; Beach, *Nature* 336:701-704, 1993). These inhibitors include $p16^{INK4}$ (an inhibitor of cyclin dependent kinase4/D1), $p21^{CIP1}$ (a general cyclin dependent kinase inhibitor), and $p27^{KIP1}$ (a specific cyclin dependent kinase2/E inhibitor). A recent crystal structure of p27 bound to cyclin dependent kinase2/A revealed how these proteins effectively inhibit the kinase activity through multiple interactions with the cyclin dependent kinase complex (Pavletich, *Nature* 382:325-331, 1996). These proteins help to regulate the cell cycle through specific interactions with their corresponding cyclin dependent

kinase complexes. Cells deficient in these inhibitors are prone to unregulated growth and tumor formation.

Schmidt et al. describe in U.S. Pat. No. 3,211,731 (issued Oct. 12, 1965) pyrazolo[3,4-d]pyrimidines of the formula:



where:

R_1 represents hydrogen, alkyl, cycloalkyl, aralkyl, oxalkyl, hydroxyalkyl, halogenoalkyl, cycloalkylalkyl, heteroaralkyl, mono- or binuclear aryl or heteroaryl;

R_3 represents hydrogen or lower alkyl;

R_6 represents substituted or unsubstituted aralkyl or heteroaralkyl.

These compounds are claimed to have utility as coronary dilating agents. Schmidt et al. disclose as intermediates, in U.S. Pat. No. 3,211,732 (issued Oct. 12, 1965) pyrazolo[3,4-d]pyrimidines within the above scope.

The two references cited above do not describe compounds in which the R^1 group is a substituted phenyl or pyridyl.

SUMMARY OF THE INVENTION

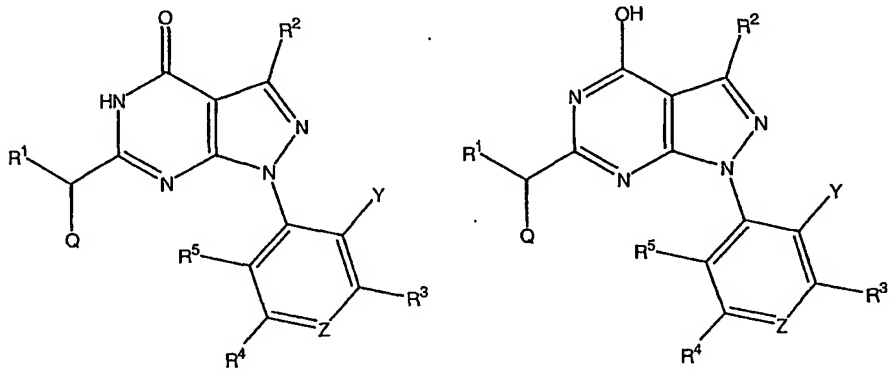
The present invention is directed to 6-substituted pyrazolo [3,4-d] pyrimidin-4-ones or pharmaceutically acceptable salt or prodrug forms thereof, that are inhibitors of the class of enzymes known as cyclin dependent kinases.

The present invention is also directed to methods of treating cancer or other proliferative diseases by administering a therapeutically effective amount of at

least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof to a patient in need of such treatment.

Additionally the present invention is directed to methods of treating cancer or other proliferative diseases, which comprises administering a therapeutically effective combination of at least one of the compounds of the present invention and at least one other known anti-cancer or anti-proliferative agent.

Compounds of the present invention have formula (I), alternatively represented by the tautomer (II):



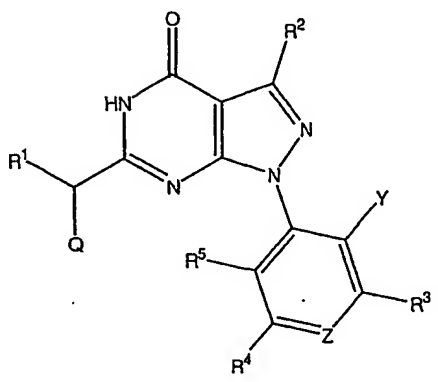
(I) (II)

wherein R^1, R^2, R^3, R^4, R^5, Q, Y, and Z as defined below or pharmaceutically acceptable salts thereof, are cyclin dependent kinase inhibitors.

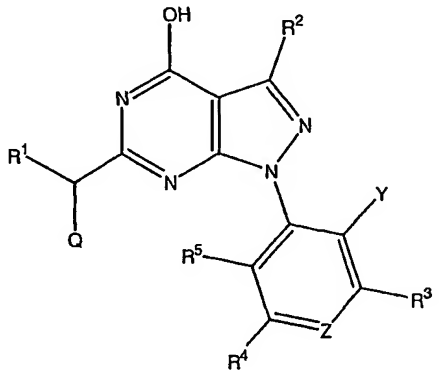
As described herein, the inhibitors of this invention are capable of inhibiting the cell-cycle machinery and consequently would be useful in modulating cell-cycle progression, which would ultimately control cell growth and differentiation. Such compounds would be useful for treating subjects having disorders associated with excessive cell proliferation, such as cancer, psoriasis, immunological disorders involving unwanted leukocyte proliferation, in the treatment of restenosis and other smooth muscle cell disorders, and the like.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a class of compounds of formula (I) or it's tautomer, formula (II):



(I)



(II)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

Q is selected from the group consisting of: H, OH, and C_{1-7} alkyl;

Y is selected from the group consisting of: F, Cl, Br, and I;

Z is selected from the group consisting of: N, C-H, C-F, C-Cl, C-Br, C-I, C-CF_3, C-NO_2, C-C_{1-4} alkyl optionally containing from 1-8 substitution groups, C-C_{2-4} alkenyl optionally containing from 1-8 substitution groups, C-C_{2-4} alkynyl optionally containing from 1-8 substitution groups, C-C_{1-4} alkoxy optionally containing from 1-8 substitution groups, C-CO_2H, C-CHO, C-$CONR^6R^9$, C-CO_2C_{1-3} alkyl, C-$C(O)C_{1-2}$ alkyl, C-CH_2NHR^6, C-$CONR^6NR^6R^9$, C-NR^6R^9; C-$SO_2NR^6R^9$, C-$CR=NNR^6R^9$, C-$CR^6=NOR^6$, and C-R^6;

R^1 is selected from the group consisting of aryl and 5-10 membered aromatic heterocycle containing from 1-4 heteroatoms selected from O, N, and S, and wherein the aryl or the 5-10 membered aromatic heterocycle is optionally substituted with 1-5 R^7 groups;

R^2 is selected from the group consisting of: C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, S-C_{1-3} alkyl, O-C_{1-3} alkyl, NH_2, NH-C_{1-3} alkyl, N(C_{1-2} alkyl)$_2$, OCF_3, cyclopropyl optionally containing from 1-4 substitution groups, cyclobutyl, cyclopropylmethyl, cyclobutylmethyl, 1-methylcyclopropyl, 1-methylcyclobutyl, CH_2CN, CH_2OH, CH_2OCH_3, CH_2NH_2, CH_2NHC_{1-3} alkyl, CH_2NMe_2, CF_3, CHO, OCH_2CH_2OH, OCH(Me)CH_2OH, OCH_2CH(Me)OH, $OCH_2CH_2NMe_2$, and CHF_2;

R^3 is selected from the group consisting of: H, F, Cl, Br, I, CF_3, CHO, CHR^6OH, $COCF_3$, CH=NOH, $CH=NOCH_3$, $CH=NNH_2$, CH=NNHMe, $CH=NNMe_2$, $CH=CHR^6$, C_{1-3} alkyl, C_{1-3} alkoxy, CO_2H, $CONH_2$, CONH(C_{1-3} alkyl), $CONR^6R^9$, CO_2C_{1-3} alkyl, C(O)C_{1-2} alkyl, NH_2, NHR^6, and NR^6R^9;

R^4 is selected from the group consisting of: H, F, Cl, Br, I, CF_3, C_{1-3} alkyl, C_{2-3} alkenyl, NH_2, NHR^6, and NR^6R^9;

R^5 is selected from the group consisting of: H, C_{1-3} alkyl, F, Cl, Br, I, CF_3, and C_{2-3} alkenyl;

R^6 and R^9 are independently, at each occurrence, the same or different, and are selected from the group consisting of: H, C_{1-8} alkyl optionally containing from 1-8 substitution groups, and C_{3-7} cyclo-alkyl,

alternatively, R^6 and R^9, together with the atoms to which they are attached, form a heterocycle having 5-7 atoms in the ring and containing 0-1 additional N, O, or S atom; or, R^6 and R^9, together with the atoms

to which they are attached, form a bicyclic heterocycle having 9-11 atoms in the ring and containing one additional N, S, or O atom; or, R^6 and R^9, together with the atoms to which they are attached, form a 5-7 membered ring and containing 0-3 additional N, S, or O atoms;

R^7 is independently, at each occurrence, selected from the group consisting of: OH, C_{1-6} alkoxy, OC_{2-6} alkyl-CO_2H, O-C_{2-6}-alkyl-NR^6R^9, F, Cl, Br, I, CF_3, OCF_3, -CN, $-NO_2$, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^6R^9$, $NR^6CONHOR^6$, $NR^6CONHSO_2R^6$, $NHNR^6C(O)OR^6$, $NR^6C(O)NR^6R^9$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $-SO_2NR^6R^9$, $NHSO_2NHCO_2C_{1-4}$ alkyl, $NR^6SO_2NR^6R^9$, $NR^6SO_2CHR^6CH_2NR^6R^9$, $NR^6COCHR^6NR^6R^9$, $NR^6COCHR^6NR^6CHR^6R^9$, $NR^6COCH_2CHR^6NR^6R^9$, $NR^6COCHR^6CH_2NR^6R^9$, $NR^6CO(CH_2)_mNR^6R^9$, $NR^6CONR^5(CH_2)_nNR^6R^9$, $NR^6CO_2(CHR^6)_nNR^6R^9$, $CONR^6NR^6R^9$, $NR^6CONR^6NR^6R^9$, C_{3-10} carbocycle, $NHCONR^6$, $NHCONHCH_2R^6$, $NHCOR^6$, $NHCOCH_2R^6$, C_{1-10} alkyl optionally substituted with 1-5 substitution groups, C_{2-10} alkenyl optionally substituted with 1-5 substitution groups, C_{2-10} alkynyl optionally substituted with 1-5 substitution groups, and C_{3-10} heterocycle containing 1-4 heteroatoms selected from O, N, and S;

R^8 is independently, at each occurrence, selected from the group consisting of: =O, OH, C_{3-6} cycloalkyl, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, F, Cl, Br, I, CO_2H, COR^6, CO_2(benzyl), $CO_2(C_{1-6}$ alkyl), and $CONR^6R^9$;

n at each occurrence is independently selected from 2, 3, 4, 5, and 6; and,

m at each occurrence is independently selected from 3, 4, 5, and 6.

The term "alkyl" is intended to include both C_{1-10} branched and straight-chain saturated aliphatic

hydrocarbon groups having the specified number of carbon atoms. Examples of alkyl include but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n- and s- hexyl, n-and s-heptyl, and, n- and s- octyl.

For purposes of the present invention the term "alkenyl" is defined as a C_{2-10} branched or straight-chain unsaturated aliphatic hydrocarbon groups having one or more double bonds between two or more carbon atoms. Examples of alkene groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and nonenyl and the corresponding C_{2-10} dienes, trienes and quadenes. The term "alkynyl" is defined as a C_{2-10} branched or straight-chain unsaturated aliphatic hydrocarbon groups having one or more triple bonds between two or more carbon atoms. Examples of alkynes include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl and nonynyl.

The term "substitution groups" means that one or more hydrogens on the molecule or atom modified by the words "optionally containing" are replaced with 1, 2, 3, 4, 5, 6, 7, 8 or 9 substitution groups provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Such "substitution groups" may be selected from the group consisting of H, -OH, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, -OR, $-NH_2$, -NHR, -NR'R, -COOH, -COOR, -CONHR, -CONR'R, -CHO, -CRO, $-SC_{1-8}$ alkyl, -halo, -CN, $-NO_2$, $-SO_2$, phosphoryl, imino, sulfhydryl, alklthio, thioester, carbocyclic, aryl, heteroaryl, bicyclic and tricyclic groups. When a substitution group is a keto (i.e., =O) group, then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. The terms R and R' refer to substitution groups, which may be the same or different and may be selected from H, -OH, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-NH_2$, -COOH, -CHO, $-SC_{1-}$

$_{8}$ alkyl, -halo, -CN, $-NO_2$, $-SO_2$, carbocyclic, aryl, heteroaryl, bicyclic and tricyclic structures.

The scope of the present invention is intended to include all permutations and combinations of the substitution groups on the backbone structure specified by formulas I and II above with the proviso that each permutation or combination can be selected by specifying the appropriate R or substitution groups.

Thus, for example, the term "C_{1-10} alkyl optionally containing from 1-8 substitution groups" refers to alkyl moieties containing saturated bonds or having one or more hydrogens replaced by, for example, halogen, hydroxyl, carbonyl, alkoxy, ester, ether, cyano, phosphoryl, amino, imino, amido, sulfhydryl, alklthio, thioester, sulfonyl, nitro, heterocyclo, aryl, or hetero-aryl.

The terms "halo" or "halogen" as used herein refer to fluoro, chloro, bromo and iodo.

The term "aryl" is intended to mean an aromatic moiety containing the specified number of carbon atoms, such as, but not limited to phenyl, tropone, indanyl or naphthyl.

The terms "cycloalkyl" and "bicycloalkyl" are intended to mean any stable ring system, which may be saturated or partially unsaturated. Examples of such include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]nonane, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane,

fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated, unsaturated or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. In this regard, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl,

carbazolyl, 4a*H*-carbazolyl, β-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The term "independently selected from", "independently, at each occurance" or similar language, means that the labeled R substitution group may appear

more than once and may be the same or different when appearing multiple times in the same structure. Thus if the labeled R^6 substitution group appears four times in a given permutation of Formula I, then each of those labeled R^6 substitution groups may be, for example, a different alkyl group falling within the definition of R^6.

In one embodiment of the present invention, the compound of formula (I) or formula (II) is selected from:

a) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-hydroxy-3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

b) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

c) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-hydroxy-4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

d) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

e) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

f) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

g) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-acetamidobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

h) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(*N*-(*t*-butoxycarbonyl)glycinamido)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

i) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(2-(*N*,*N*-dimethylamino)ethylaminocarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

j) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-amino-2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

k) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(pyrid-2-ylmethylaminocarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

l) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-glycinamidobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

m) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(pyrid-4-ylmethylaminocarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

n) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(*para*-biphen-4-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

o) 1-(2,6-dichlorophenyl)-3-ethyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

p) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(4-methylpiperazin-1-ylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

q) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(dimethylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

r) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(2-(hydroxymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

s) 1-(2,6-dichlorophenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

t) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(methoxyaminocarbonylmethyl)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

u) 1-(2,6-dichlorophenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

v) 1-(2,6-dichlorophenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

w) 1-(2-chloro-6-methylphenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

x) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3,5-dihydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

y) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-hydroxy-3-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

z) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-amino-3-nitrobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

aa) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(methylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ab) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-(methane sulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ac) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(methane sulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ad) 1-(2,6-dichloro-4-(pyrid-3-ylaminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ae) 1-(2,6-dichloro-4-(pyrid-4-ylaminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

af) 1-(2,6-dichloro-4-(cyclopropylaminocarbonyl) phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d] pyrimidin-4-one;

ag) 1-(2,6-dichloro-4-(*N*-(pyrid-3-ylmethyl) aminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl) pyrazolo[3,4-d]pyrimidin-4-one;

ah) 1-(2,6-dichloro-4-(*N*-(pyrid-2-ylmethyl) aminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl) pyrazolo[3,4-d]pyrimidin-4-one;

ai) 1-(2,6-dichloro-4-(ethylaminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

aj) 1-(2,6-dichloro-4-(benzylaminocarbonyl)phenyl)-3-ethyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ak) 1-(2,6-dichloro-4-(2-(dimethylamino)ethylamino carbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

al) 1-(2,6-dichloro-4-(methylaminocarbonyl)phenyl)-3-ethyl-6-(4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

am) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-(*N*,*N*-dimethylglycinamido)-2-methylbenzyl)pyrazolo[3,4-d] pyrimidin-4-one;

an) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(*N*,*N*-dimethyl glycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ao) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(*N*-methylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ap) 1-(2,6-dichloro-4-bromophenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

aq) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methoxycarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ar) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

as) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-hydroxy-4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

at) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

au) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(methanesulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

av) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(difluoroacetamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

aw) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(acetamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ax) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(methylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ay) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

az) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(azetidin-3-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ba) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-aminoethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bb) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(isopropylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bc) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-fluorobenzylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bd) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(pyrrolidin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

be) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(pyrid-2-ylmethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bf) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(*t*-butoxycarbonylamino)ethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bg) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(pyrid-3-ylmethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bh) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(pyrid-4-ylmethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bi) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(morpholin-4-yl)ethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bj) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(methylaminocarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bk) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(ethylaminocarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bl) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(piperazin-1-ylcarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bm) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-methylpyrid-3-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

bn) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethylaminocarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bo) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2,2-dimethylhydrazin-1-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bp) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1-hydroxybut-4-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bq) (+/-)1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-hydroxyprop-1-ylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

br) (+/-)1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1-hydroxyprop-2-ylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bs) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(pyrid-3-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

bt) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bu) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(dimethylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bv) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(pyrid-4-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

bw) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*,*N*-dimethylglycinamido)-3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bx) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*,*N*-dimethylglycinamido)-3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

by) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methylaminocarbonylamino)-3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bz) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-(3-(dimethylamino)propyl)aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ca) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(benzoxazol-2-on-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

cb) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylcarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cc) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl,*N*-(2-(dimethylamino)ethyl)aminocarbonylmethyl)benzyl)-pyrazolo[3,4-d]pyrimidin-4-one;

cd) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methylaminocarbonylamino)-3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ce) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylmethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

cf) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(piperazin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

cg) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(morpholin-4-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

ch) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(imidazol-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

ci) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)aminomethylcarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cj) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(cyclopropylaminomethylcarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

ck) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*,*N*-dimethylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cl) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

cm) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-aminoindazol-5-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

cn) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl,*N*-(2-(dimethylamino)ethyl)aminomethylcarbonyl amino)benzyl)-pyrazolo[3,4-d]pyrimidin-4-one;

co) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylcarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cp) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(azetidin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cq) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-hydroxy-4-(imidazol-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cr) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cs) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(3-(dimethylamino)prop-1-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ct) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylhomopiperazin-1-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cu) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-2-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cv) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*t*-butoxycarbonylaminosulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cw) 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cx) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(morpholin-4-yl)ethylaminothiocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cy) 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-(*N,N*-dimethylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cz) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-bromobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

da) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(piperazin-2-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

db) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1,4-dimethylpiperazin-2-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dc) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethylsulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dd) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-amino-3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

de) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-hydantoin-3-ylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

df) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(2H-1,4-benzoxazin-3-on-7-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

dg) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-(2-(dimethylamino)ethyl)aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dh) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-hydroxyethylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

di) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dj) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dk) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-glycinamidobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dl) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dm) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dn) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-(aminomethyl)piperidin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

do) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(homopiperazin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dp) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(ethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dq) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(dimethylaminomethyl)-3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dr) (*S*)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methylprolinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ds) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-,*N*-dimethylalaninamido)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

dt) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1,4,7-triazacyclonon-1-ylmethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

du) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-amino-2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dv) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(morpholin-4-yl)ethylaminocarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

dw) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(*N*-,*N*-dimethylglycinamido)-2-methylbenzyl)pyrazolo[3,4-d] pyrimidin-4-one;

dx) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylaminocarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

dy) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(morpholin-4-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

dz) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methoxyaminocarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

ea) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methanesulfonamidocarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

eb) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl,*N*-(2-(dimethylamino)ethyl)aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ec) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl,*N*-(1-methylpiperidin-4-yl)aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ed) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(tetrahydrofur-2-ylmethylaminocarbonylamino)benzyl)-pyrazolo[3,4-d]pyrimidin-4-one;

ee) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1-hydroxypent-2-ylaminocarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

ef) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1-hydroxyprop-2-ylaminocarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

eg) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-hydroxyprop-1-ylaminocarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

eh) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)prop-1-ylaminocarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

ei) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(3-hydroxy-4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ej) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(indazol-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

ek) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(indazol-5-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

el) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(indazol-4-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

em) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(benz oxazol-2-on-5-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

en) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(3-hydroxy-4-nitrobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

eo) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ep) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(4-(*N,N*-dimethylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

eq) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*cis*-3,4-dimethylpiperazin-1-ylmethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

er) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*trans*-2,5-dimethylpiperazin-1-ylmethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

es) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(3-methylpiperazin-1-ylmethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

et) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(5-(dimethylaminomethyl)-1-methylpyrrol-2-yl)pyrazolo[3,4-d]pyrimidin-4-one;

eu) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylaminocarbony)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ev) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(*N*-methyl, *N*-(2-(dimethylamino)ethyl)aminocarbonylamino) benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ew) 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-(*N*-methyl,*N*-(1-methylpiperidin-4-yl)aminocarbonylamino) benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ex) 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)aminomethylcarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ey) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(*N*-methyl,*N*-((3*S*, 4*S*)-4-dimethylaminotetrahydrofur-3-yl)aminocarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ez) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(*N*-methyl, *N*-(2-(dimethylamino)ethyl)aminocarbonyl) benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fa) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-pyrrolidin-1-ylethylaminocarbonyamino)benzyl)pyrazolo [3,4-d] pyrimidin-4-one;

fb) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl, *N*-(2-(dimethylamino)ethyl)aminocarbonymethyl)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

fc) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(*N*-(2-(di methylamino)ethyl)aminocarbonymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fd) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-(2-(dimethylamino)ethyl)aminocarbonyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fe) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ff) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)aminocarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fg) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl, *N*-(2-(dimethylamino)ethyl)aminocarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fh) 1-(2,6-dichloro-4-sulfonamidophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one; and

fi) 1-(4-aminomethyl-2, 6-dichlorophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one.

The skilled artisan will understand that all forms of the organic compounds set forth in the present invention are intended to fall within the scope of the present invention, including, but not limited to, pharmaceutically acceptable salts, prodrugs, isomers, enantiomers and crystal forms.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and

the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, EtOAc, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, the disclosure of which is hereby incorporated by reference, in it's entirity as though set forth in full..

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

"Prodrugs", as the term is used herein, is intended to include any covalently bonded carriers which release an active parent drug of the present invention in vivo when such prodrug is administered to a mammalian subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (i.e., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form.

Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same, and compositions containing the same. Prodrugs of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

The term "therapeutically effective amount" of a compound of the present invention means an amount effective to inhibit the action of the class of enzymes known as cyclin dependent kinases or treat the symptoms of cancer or other proliferative diseases in a host.

As used herein, the term "anti-cancer" or "anti-proliferative" agent includes, but is not limited to, altretamine, busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, thiotepa, cladribine, fluorouracil, floxuridine, gemcitabine, thioguanine, pentostatin, methotrexate, 6-mercaptopurine, cytarabine, carmustine, lomustine, streptozotocin, carboplatin, cisplatin, oxaliplatin, iproplatin, tetraplatin, lobaplatin, JM216, JM335, fludarabine, aminoglutethimide, flutamide, goserelin, leuprolide, megestrol acetate, cyproterone acetate, tamoxifen, anastrozole, bicalutamide, dexamethasone, diethylstilbestrol, prednisone, bleomycin, dactinomycin, daunorubicin, doxirubicin, idarubicin, mitoxantrone, losoxantrone, mitomycin-c, plicamycin, paclitaxel, docetaxel, topotecan, irinotecan, 9-amino camptothecan,

9-nitro camptothecan, GS-211, etoposide, teniposide, vinblastine, vincristine, vinorelbine, procarbazine, asparaginase, pegaspargase, octreotide, estramustine, and hydroxyurea.

The compounds of the present invention may contain one or more asymmetrically substituted carbon atoms or chiral centers, and may be isolated in optically active or racemic forms. The skilled artisan will appreciate that it is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

The present invention is intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include ^{13}C and ^{14}C.

DOSAGE AND FORMULATION

In another embodiment, the present invention provides a novel pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) or (II) or a pharmaceutically acceptable salt form thereof.

The cyclic dependent kinase inhibitor compounds of this invention can be administered as treatment for cancer or proliferative diseases by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be

administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but preferably are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. A daily dosage of active ingredient can be expected to be about 0.001 to about 1000 milligrams per kilogram of body weight, with the preferred dose being about 0.1 to about 30 mg/kg.

Dosage forms of compositions suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, suppositories and powders, or in liquid dosage forms, such as elixirs, syrups and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the

atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts, and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben and chlorobutanol. Suitable pharmaceutical carriers and administration forms, as well as their methods of manufacture are described in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, a standard reference text in this field, the disclosure of which is hereby incorporated by reference.

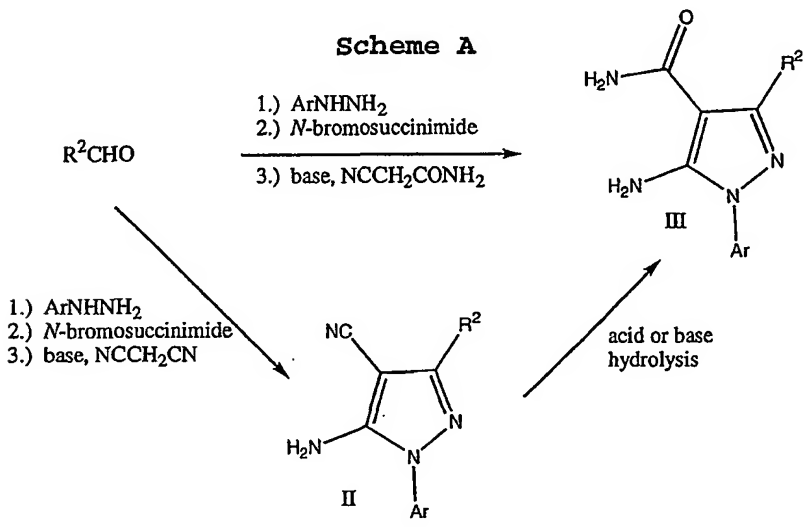
SYNTHESIS

The compounds of the present invention can be synthesized using the methods described below, and/or with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Each of the references cited below are hereby incorporated herein by reference.

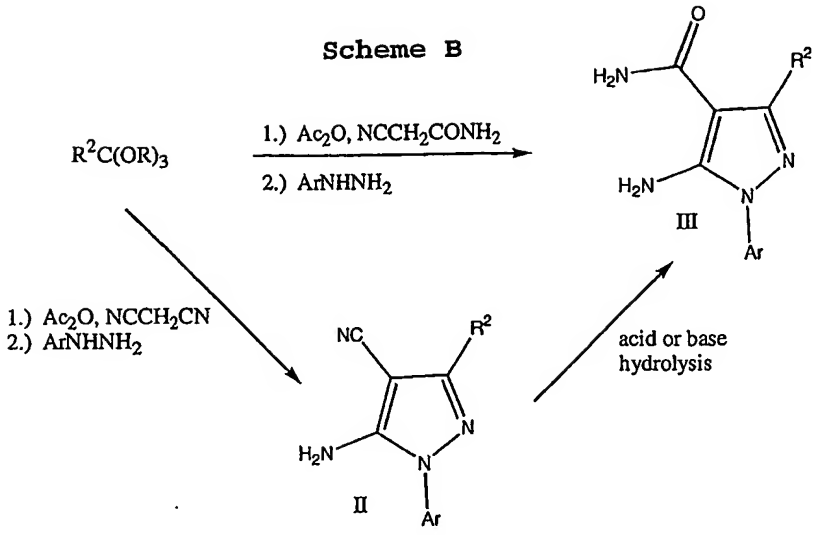
Key intermediates preparing the compounds of the present invention are pyrazole aminonitriles, aminocarboxamides, and aminoesters of the formulas II, III, and IV, respectively. The preparation of these intermediates is has precedence in the chemical

literature, and several methods are summarized in Schemes A (A. O. Abdelhamid, A. S. Shawali, et al. *J. Heterocycl. Chem.*, 1984, *21*, 1049.); B (C. C. Cheng and R. K. Robins, *J. Org. Chem.* 1956, *21*, 1240.); C (P. Schmidt and J. Druey, *Helv. Chem. Acta*, 1956, *39*, 986.); and D (Tominaga et al., *J. Heterocycl. Chem.*, 1990, *27*, 775). A wide variety of starting hydrazines and aldehydes are commercially available or can be prepared by standard organic transformations. The substituents in the following schemes, which are designated R^1, R^2, and Q, have the same definition as that defined above in the Detailed Description.

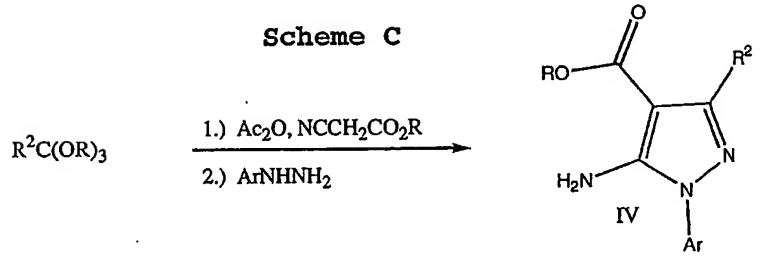
Scheme A



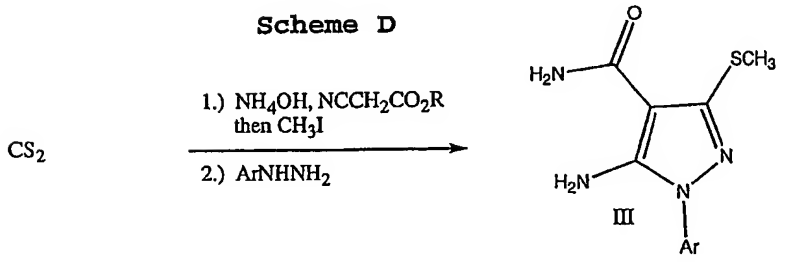
Scheme B



Scheme C



Scheme D

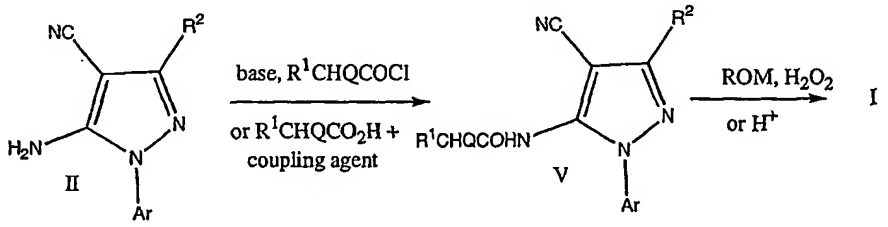


Aminonitriles of the formula II can be converted to pyrazolo[3,4-d]pyrimidines of the present invention as shown in Scheme E. In summary, the aminocarboxamide is acylated, optionally in the presence of a suitable solvent such as dichloromethane by treatment with a

suitable base such as triethylamine followed by an acid halide of the formula $R^1CHQCOX$, preferably an acid chloride to give carboxamidonitriles of the formula V. Alternately carboxamidonitriles of the formula V can be prepared by coupling of aminonitriles II with carboxylic acids of the general formula R^1CHQCO_2H in the presence of a suitable base and coupling reagent in a suitable solvent. The coupling of amines and carboxylic acids has been reviewed (Klausnew and Bodansky *Synthesis*, 1972, 453-463), and the variety of reagents available for effecting it can be appreciated by those skilled in the art.

Transformation of carboxamidonitriles of the formula V to the compounds of the present invention can be accomplished by treatment with an excess of hydrogen peroxide in the presence of a suitable base, preferably a metal hydroxide or alkoxide base in a solvent, preferably water, an alcohol, or a water-alcohol mixture at a temperature in the range of about 0 °C up to 100 °C.

Scheme E

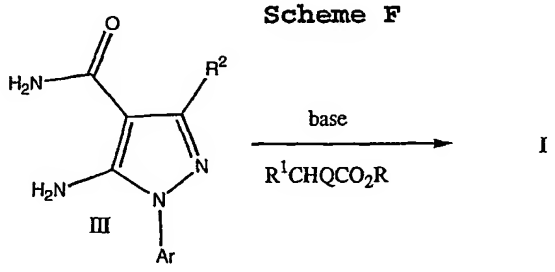


Alternatively, carboxamidonitriles of the formula V can be transformed to the compounds of the present invention by heating, preferably for about an hour in concentrated, strong acid, preferably 85% H_3PO_4.

Scheme F shows an alternative means for preparing the compounds of the present invention. Amino carboximides of the formula III in a suitable solvent, preferably a lower alkanol, are treated with an excess of an ester of the formula R^1CHQCO_2R, where R is lower alkyl and an excess of a base, preferably a metal lower

alkoxide, preferably at the boiling point of the solvent to give compounds of the present invention. Many arylacetic esters are commercialy available or can be prepared in one step from commercially available arylacetic acids by esterification with an excess of an alcohol, ROH, preferably at reflux with ethyl or methyl alcohol, used as solvent in the presence of an acid catalyst such as H_2SO_4 or *p*-TsOH. Alternatively, a coupling reagent such as DCC can be used, preferably in a solvent such as CH_2Cl_2, with a catalylst such as DMAP. Phenylacetic acids may be prepared by acid or base hydrolysis of arylacetonitriles which in turn may be prepared by treatment of aryl halides with CN^-, preferably in solvents such as DMF, MeOH, EtOH, water, DMSO, or mixtures thereof. Further examples of arylacetic esters may be prepared from aryl carboxylic acids under Arndt-Eistert (Meier and *Zeller Angew. Chem. Int. Ed. Engl.* 1975, 14, 32-43) or related homologation conditions.

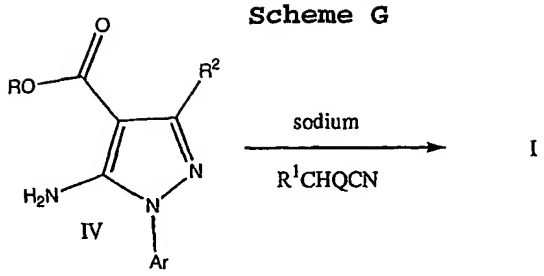
Scheme F



Wherein I represents compounds of formula I.

Aminoesters of the formula IV can be converted to compounds of the present invention by reaction with an excess of a nitrile of the formula R^1CHQCN and sodium. This reaction is preferably performed neat with heating.

Scheme G



Wherein I represents compounds of formula I

Pyrazolo[3,4-d]pyrimidin-4-ones may be further elaborated as described below to give additional compounds of the present invention. Electrophilic aromatic substitution reactions can be performed on the R^1 aryl or heteroaryl group to introduce substituents. Such reactions include, but are not limited to nitration, acylation (Friedel-Crafts), halogenation, alkylation (Friedel-Crafts), chloromethylation, sulfonation, and aminomethylation (Mannich reaction). Conditions for performing these reactions are familiar to those skilled in the art of organic synthesis, generally involving reaction of the electrophile with the aryl or heteroaryl substrate in the presence of a catalyst. In the case of nitrations or Mannich reactions, the catalyst is preferably a protic acid which may serve as solvent, where the electrophile is generated in situ from saltpeter, or an amine and a carbonyl component, respectively. For other electrophilic aromatic substitution reactions, preferred catalysts are Lewis acids, including but not limited to FeX_3, AlX_3, and ZnX_2, where X is halogen.

The compounds prepared above which have an amino group can be derivatized by reaction with electrophiles including, but not limited to acyl halides, anhydrides, isocyanates, chloroformates, sulfonyl halides, alkyl halides, lactones, or esters. Conditions for performing these addition reactions are familiar to those skilled in the art of organic synthesis, generally involving addition of the electrophile to the nucleophile,

preferably in solution at a temperature between 0 °C and RT. Addition of a base may be necessary. It should be noted that the products of these reactions can react further with some electrophiles at the pyrimidinone nitrogen (N5). The resulting functional groups (amides, carbamates, etc.) are less stable to basic hydrolysis than the desired anilino- or aliphatic groups and can be cleaved back to the pyrimidinone having H on N5. Reaction of compounds bearing an amine group with agents such as haloacyl halides, α, β - unsaturated acid halides, or halosulfonyl halides gives intermediates which can react with nucleophiles such as primary or secondary amines, diamines, alkoxides, aminoalcohols or thiols.

The compounds prepared above, which have a carboxyl group, can be derivatized by activation and reaction with nucleophiles including, but not limited to amines and alcohols to give, respectively, amides and esters. The coupling of amines and carboxylic acids with carbodiimides has been reviewed (Klausnew and Bodansky *Synthesis*, 1972, 453-463), and the variety of additional reagents available for effecting it as well as the potential need for protecting groups (Green and Wuts "Protective Groups in Organic Synthesis" Second Edition, John Wiley & Sons, 1991) to mask reactive functionality can be appreciated by those skilled in the art. The preparation of esters from acids has been described above. Reduction of these amides and esters to amines and alcohols can be performed using a suitable hydride reducing agent.

The compounds prepared above which have an amino group can be derivatized by conversion to an electrophilic species by activation with phosgene or a phosgene equivalent (*Tetrahedron: Asymmetry* 1995, *6*, 745; *J. Org. Chem.* 1994, *59*, 1937.), preferably in the presence of a base, and reaction with nucleophiles including, but not limited to amines, alcohols, and

sulfonamides to give, respectively, ureas, carbamates, and sulfonylureas. Conditions for performing these reactions and the hazards associated with handling phosgene and phosgene equivalents are familiar to those skilled in the art of organic synthesis, and all appropriate precautions should be taken.

Further transformations which may be required to prepare compounds of the present invention include reductions of ketones, aldehydes, esters, acids, amides or reductive aminations by alumino- and borohydride reagents (J. Seyden-Penne "Reductions by the Alumino and Borohydrides in Organic Synthesis" VCH Publishers, Inc., 1991) and oxidations of groups including but not limited to alcohols, aldehydes, olefins, thioethers, sulfoxides, and heteroaryl groups (Milos Hudlicky "Oxidations in Organic Chemistry" American Chemical Society, 1990). Reduction of functional groups such as alkenes, alkynes, nitrogen, nitro- or cyano- groups could be accomplished by catalytic hydrogenation or by dissolving metal reduction. Further elaboration of intermediates containing electrophilic sites to compounds of the present invention could be accomplished by displacement with nucleophiles including, but not limited to, CN^-, amines, alkoxides, mercaptans, or carbanions. Still other compounds of the present invention could be prepared by coupling of aryl halides, triflates, or stannames with the appropriate boronic acids (Stilk, J.K. *Angew. Chem. Int. Ed. Engl.* 1986, 25, 508; Suzuki, A. *Pure Appl. Chem.* 1985, 57, 1749). The compounds prepared above, which have a carbonyl group, can be derivatized further by reaction with nucleophiles to give secondary alcohols. Such nucleophiles include, but are not limited to, Grignard reagents, alkyl-, alkenyl-, and alkynyl-lithium reagents, and allyl- stannanes, silanes, and the like. Compounds prepared as described above could be further elaborated by rearrangements such as the Beckmann

(Gawley in *Org. React.* 1988, *35*, 1-420) or other rearrangements.

Further elaboration of the compounds prepared above can be accomplished by generation of an organomagnesium organolithium species by directed metallation (Beak and Meyers *Acc. Chem. Res.* 1986, *19*, 356-363; Beak and Snieckus *Acc. Chem. Res.* 1982, *15*, 306-312; Katritzky, Lam, and Sengupta Prog. *Heterocycl. Chem.* 1989, *1*, 1-29) or from an aryl halide by lithium-halogen exchange (Parham and Bradsher, *Acc. Chem. Res.* 1982, *15*, 300-305).

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Abbreviations used in the Examples are defined as follows: "°C" for degrees Celsius, "MS or mass spec." for mass spectrum, "g" for gram or grams, "h" for hour or hours, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "mmol" for millimoles, "M" for molar, "min" for minute or minutes, "DMF" for dimethylformamide, "THF" for tetrahydrofuran, "Boc" for *t*-butoxycarbonyl, "Bop" for (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate, "EDC" for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, "BopCl" for bis(2-oxo-3-oxazolidinyl)phosphinic chloride, "ether" for diethyl ether, "aq" for aqueous, "RT" for ambient temperature, "HOAc" for acetic acid, "EtOAc" for ethyl acetate "*p*-TsOH" for *para*-toluenesulfonic acid, "DIEA" for *N, N*-diisopropylethylamine, "*t*-BuOH" for *t*-butanol, "EtOH" for ethanol, "MeOH" for methanol, "NBS" for *N*-bromosuccinimide, and "TFA" for trifluoroacetic acid. "Mass spec." results refer to M/z for the product species composed entirely of the most prevalent isotopes of each of its constituent atoms, i.e. 12 for carbon, 1 for

hydrogen, 35 for Cl, 14 for N, and 16 for O. Ionization techniques used give M^+, $(M+H)^+$, or $(M-H)^-$ species. Proton (^1H) nuclear magnetic resonance(NMR) experiments were performed on dilute solutions in the solvent indicated at the frequency (generally 300 MHz) indicated. Chemical shifts are reported in ppm downfield from tetramethylsilane. The following abbreviations are used: "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, and "br." for broad. Reported integrations are approximate. It is understood by those experienced in the interpretation of NMR spectra that some proton signals are absent, increased or diminished in measured intensity in a given spectrum due to factors such as poor instrument phase, rapid exchange with trace water or protons in the solvent, or because they resonate at a frequency outside that recorded (generally -0.2 to +15 ppm). It is also understood that chemical shifts for a given compound may vary due to factors such as concentation or pH of the sample. It is further understood that due to the precision in measurement of coupling constants, signals for coupled protons may have coupling constants that differ slightly.

Example 1

1-(2,4,6-Trichlorophenyl)-3-(methylthio)-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 176 mg (0.5 mmol) of 5-amino-3-(methylthio)-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide in 6 mL of absolute ethanol was added 550 mg (3.0 mmol) of 3-methoxyphenylacetyl chloride followed by 2.3 mL (6.0 mmol) of 2.66 M sodium ethoxide in ethanol. The solution was stirred 18 h at reflux, and the heating mantle was then removed. The reaction was treated with 5 mL of 10% aq. HOAc, cooled to ambient temperature, and filtered. The filtrate was washed with 6 mL of 1:1 water-methanol then 6 mL of 1:1 ether-hexanes. The off-white solid was briefly air-dried to give 220 mg (92%) of

1-(2,4,6-trichlorophenyl)-3-(methylthio)-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one, mp 245-248 °C. Mass spec. Calc'd for $C_{20}H_{16}N_4O_2SCl_3$: 481.0060. Found: 481.0076 $(M+H)^+$.

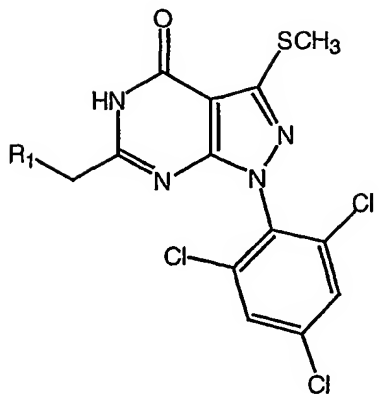
Example 2

1-(2,4,6-Trichlorophenyl)-3-(methylthio)-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 55 mg (0.11 mmol) of 1-(2,4,6-trichlorophenyl)-3-(methylthio)-6-(3-methoxy benzyl)pyrazolo[3,4-d]pyrimidin-4-one in 2 mL of CH_2Cl_2 was added 1 mL (1 mmol) of 1 M boron tribromide in CH_2Cl_2. The solution was stirred 35 min. at ambient temperature, and it was then cooled to 0 °C. The reaction was quenched with 4 mL of 1 M aq. HCl. The mixture was poured into water and extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford 52 mg (98%) of 1-(2,4,6-trichlorophenyl)-3-(methylthio)-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one as an off-white solid, m.p. 264-266 °C. Mass spec. Calc'd for $C_{19}H_{13}N_4O_2SCl_3$: 465.9825(M)$^+$. Found: 465.9798.

Starting from 5-amino-3-(methylthio)-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide, the following compounds were prepared by methods similiar to those used to synthesize the compounds above:

Table I



Ex. #	R^1	m.p. (°C)	MS
3	phenyl	234-238	
4	imidazol-4-yl		441
5	4-pyridyl	283-287	452
6	3,4-dimethoxyphenyl	226-230	511
7	3-nitrophenyl	243-255	496
8	4-methoxyphenyl	263-267	
9	4-hydroxyphenyl	294-296	467
10	2,5-dimethoxyphenyl	137-150	481
11	2,5-dihydroxyphenyl		483
12	4-aminophenyl		466
13	3,4-methylenedioxyphenyl	257-260	
14	2-thienyl	218-222	457

Example 15

1-(2,4,6-Trichlorophenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

Part A: To a stirred solution of 320 mg (1.9 mmol) of 2-cyano-3-ethoxypentenamide in 7 mL of MeOH was added 465 mg (2.2 mmol) of 2,4,6-trichlorophenylhydrazine. The solution was stirred 3 h at reflux, treated with 2 mL of water, and allowed to stir an additional 1 h, cooling to RT. The white solid which precipitated was filtered, washed with 2:1 MeOH-water, and air-dried to afford 520 mg (82%) of 5-amino-3-ethyl-1-(2,4,6-trichlorophenyl)

pyrazole-4-carboxamide, mp 186-188 °C, Mass Spec(CI+): 331.9989(M)$^+$.

Part B: To a stirred solution of 167 mg (0.5 mmol) of 5-amino-3-ethyl-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide in 6 mL of absolute ethanol was added 550 mg (3.0 mmol) of 3-methoxyphenylacetyl chloride followed by 2.3 mL (6.0 mmol) of 2.66 M sodium ethoxide in ethanol. The solution was stirred 18 h at reflux, and the heating mantle was then removed. The reaction was treated with 5 mL of 10% aq. HOAc, cooled to ambient temperature, and filtered. The filtrate was washed with 6 mL of 1:1 water-methanol then 6 mL of 1:1 ether-hexanes. The off-white solid was briefly air-dried to give 170 mg (76%) of 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-methoxybenzyl) pyrazolo[3,4-d]pyrimidin-4-one, mp 235-238 °C. Mass Spec. 463(M+H)$^+$.

Example 16

1-(2,4,6-Trichlorophenyl)-3-ethyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 80 mg (0.17 mmol) of 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-methoxybenzyl) pyrazolo[3,4-d]pyrimidin-4-one in 1 mL of CH_2Cl_2 was added 1 mL (1 mmol) of 1 M boron tribromide in CH_2Cl_2. The solution was stirred 1 h at ambient temperature and then cooled to 0 °C. The reaction was quenched with 4 mL of 1 M aq. HCl. The mixture was poured into water and extracted with 1:1 tetrahydrofuran-EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford 77 mg (100%) of 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one as an off-white solid. Mass Spec.: 449(M+H)$^+$.

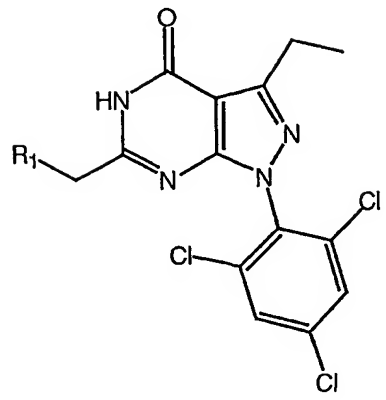
Example 17

1-(2,4,6-Trichlorophenyl)-3-ethyl-6-(4-(4-methoxyphenyl)benzyl))pyrazolo[3,4-d]pyrimidin-4-one

To a stirred mixture of 100 mg (0.2 mmol) of 1-(2, 4, 6-trichlorophenyl)-3-ethyl-6-(4-bromobenzyl) pyrazolo[3, 4-d]pyrimidin-4-one and 38 mg (0.25 mmol) of 4-methoxyphenylboronic acid in 10 mL of toluene, 0.5 mL of EtOH, and 2 mL of 2 M Na_2CO_3 was added to 5 mg of $Pd(Ph_3P)_4$. The mixture was heated to reflux overnight, poured into water, and extracted with $CHCl_3$. The organic extract was dried ($MgSO_4$), filtered through celite, chromatographed (elution with 5% $MeOH/CH_2Cl_2$), and recrystallized to afford 64 mg (59%) of 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(4-methoxyphenyl)benzyl) pyrazolo[3,4-d]pyrimidin-4-one as a pale brown powder, mp 275-277 °C, Mass spec.: 537 $(M-H)^-$.

Starting from 5-amino-3-ethyl-1-(2,4,6 trichlorophenyl)pyrazole-4-carboxamide the following compounds were prepared by methods similiar to those used to synthesize the compounds above:

Table II



Ex. #	R^1	m.p. (°C)	MS
18	3-indolyl	296-299	474
19	3-hydroxy-4-methylphenyl	amorphous	
20	3-methoxy-4-methylphenyl	263-265	
21	4-hydroxy-3-methylphenyl	260-263	
22	4-methoxy-3-methylphenyl	245-247	479
23	phenyl	240-241	431
24	3,4,5-trimethoxyphenyl	224-226	523
25	4-bromophenyl	296-299	511
26	4-hydroxy-3-nitrophenyl	263-266	
27	2-methoxyphenyl	188-191	463
28	4-pyridyl	277-280	432
29	3-amino-2-methylphenyl	242-243	
30	3,4-dimethoxyphenyl	220-222	493
31	3,4-dihydroxyphenyl		465
32	2-pyridyl·HOAc	164-169	433
33	4-hydroxy-3-methoxyphenyl	260-280	479
34	4-methoxyphenyl	261-262	463
35	4-hydroxyphenyl	289-291	449
36	3-hydroxy-4-methoxyphenyl	237-240	479
37	3-aminophenyl	236-240	447.0418
38	4-aminophenyl	256-259	448
39	3-methylphenyl	238-240	
40	5-methoxy-3-indolyl	295-298	

41	3-amino-4-hydroxyphenyl	amorphous	464
42	3,4-dimethoxy-6-hydroxy-methylphenyl	203-205	
43	3-(dimethylaminomethyl)phenyl HCl salt	amorphous	492
44	4-amino-3-nitrophenyl	amorphous	491
45	4-(dimethylamino)phenyl		476
46	3-(ethoxycarbonylmethyl)phenyl	168-169	517
47	3-(carboxymethyl)phenyl	192-194	

Example 48

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

Part A: To a stirred solution of 106 g (500 mmol) of 2,4,6-trichlorophenyl hydrazine in 600 mL of absolute ethanol was added 48.1 mL (530 mmol) of isobutyraldehyde. The solution was stirred 2 h at RT and concentrated under reduced pressure to afford an oil. The crude oil was dissolved in 450 mL of dry DMF and cooled to 0 °C. This solution was treated with 94.3 g (530 mmol) of NBS in four portions over 10 min. The solution was stirred 1 h at 0 °C and poured onto ice. The mixture was diluted with water and extracted with 800 mL of ether. The organic extract was washed twice with water and once with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. In a separate flask, 44.3 g (670 mmol) of malononitrile in 140 mL of EtOH was cooled to 0 °C and treated with 252 mL (670 mmol) of 2.66 M NaOEt in EtOH over 6 min. This solution was added in four portions over 5 min. to a rapidly stirred solution of the crude bromohydrazone in 350 mL of absolute EtOH. Using a heat pistol, this solution was maintained at reflux for 10 min. further. The reaction was cooled, quenched with 5% aq. HOAc, and extracted twice with ether. The combined organic extracts were washed (brine), dried ($MgSO_4$) and filtered over activated charcoal and celite, and concentrated under reduced pressure. The product was

chromatographed on silica gel (gradient elution with 1:3 ether-hexanes and 2:1 ether-CH_2Cl_2) to afford 93.5 g (57%) of 5-amino-4-cyano-3-isopropyl-1-(2,4,6-trichlorophenyl)pyrazole as a white solid. ^1H NMR($CDCl_3$, 300 MHz) δ 7.51(s, 2H); 4.28(br. s, 2H); 3.05(septet, 1H, J = 7.0 Hz); 1.36(d, 6H, J = 7.0 Hz).

Part B: Thirty grams (91.0 mmol) of 5-amino-4-cyano-3-isopropyl-1-(2,4,6-trichlorophenyl)pyrazole was dissolved in 80 mL of con. H_2SO_4 and stirred 24 h at RT. The solution was added to cold aqueous NaOH, and the resulting precipitate was filtered, washed with water, and dried under vacuum to give 29.1 g (92%) of 5-amino-3-isopropyl-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49(s, 2H); 5.06-5.63(m, 4H); 3.06(septet, 1H, J = 6.8 Hz); 1.39(d, 6H, J = 6.9 Hz).

Part C: To a stirred solution of 167 mg (0.5 mmol) of 5-amino-3-isopropyl-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide in 6 mL of absolute ethanol was added 550 mg (3.0 mmol) of 3-methoxyphenylacetyl chloride followed by 2.3 mL (6.0 mmol) of 2.66 M sodium ethoxide in ethanol. The solution was stirred 18 h at reflux, and the heating mantle was then removed. The reaction was treated with 5 mL of 10% aq. HOAc, cooled to ambient temperature, and filtered. The filtrate was washed with 6 mL of 1:1 water-methanol then 6 mL of 1:1 ether-hexanes. The off-white solid was briefly air-dried to give 170 mg (76%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-methoxybenzyl) pyrazolo[3,4-d]pyrimidin-4-one, mp 204-205 °C, Mass Spec: 477(M+H)$^+$.

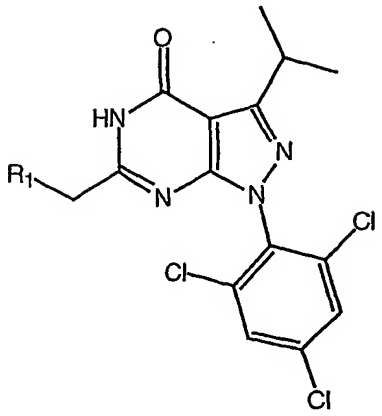
Example 49

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 65 mg (0.14 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one in 1 mL of CH_2Cl_2 was added 1 mL(1 mmol) of 1 M boron tribromide in CH_2Cl_2. The solution was stirred 1 h at ambient temperature and then cooled to 0 °C. The reaction was quenched with 4 mL of 1 M aq. HCl. The mixture was poured into water and extracted with 1:1 THF-EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford 63 mg (100%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one as an amorphous solid. ^1H NMR (300 MHz, DMSO) δ 12.46(br. s, 1H); 9.33(br. s, 1H); 7.96(s, 2H); 7.03(t, 1H, J = 7.7 Hz); 6.55-7.08(m, 3H); 3.75(s, 2H); 3.19-3.36(m, 1H); 1.29(d, 6H, J = 7.0 Hz).

Starting from 5-amino-3-isopropyl-1-(2,4,6 trichlorophenyl)pyrazole-4-carboxamide the following compounds were prepared by methods similiar to those used to synthesize the examples above:

Table III



Ex. #	R^1	m.p. (°C)	MS
50	3-hydroxy-4-methoxyphenyl		491
51	3-aminophenyl		462
52	4-aminophenyl	223-225	462
53	4-methoxyphenyl		475
54	4-amino-3-methoxyphenyl	238-240	
55	4-amino-3-hydroxyphenyl	210-217(dec.)	476
56	4-(dimethylaminomethyl)phenyl HCl salt	278-281(dec.)	
57	5-methoxy-2-methylindol-3-yl		528
58	5-hydroxy-2-methylindol-3-yl		514
59	4-bromophenyl	229-230	
60	2-pyridyl	214-215	448.0506
61	4-pyridyl	273-275	448.0502
62	4-methylphenyl	205-206	461.0696
63	2-methylphenyl	194-195	461.0700
64	3-pyridyl	214-215	448.0506
65	4-methyl-3-pyridyl	225-227	
66	3-amino-2-methylphenyl		474
67	4-(methylamino)phenyl	244-246	476
68	2H-1,4-benzoxazin-3-on-7-yl		516
69	4-chloro-3-pyridyl	245-248	480

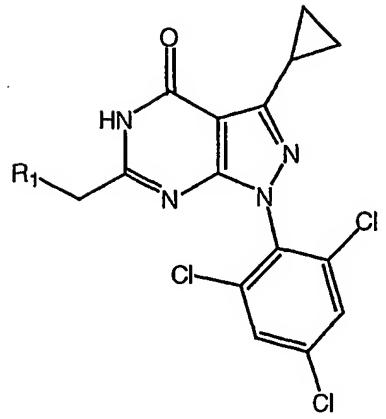
Example 70

1-(2,4,6-Trichlorophenyl)-3-cyclopropyl-6-(3-hydroxy-4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 146 mg (0.42 mmol) of 5-amino-3-cyclopropyl-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide in 6 mL of absolute ethanol was added 533 mg (2.53 mmol) of ethyl 3-hydroxy-4-methoxyphenylacetate followed by 1.91 mL (5.1 mmol) of 2.66 M sodium ethoxide in ethanol. The solution was stirred 18 h at reflux, and the heating mantle was then removed. The reaction was treated with 5 mL of 10% aq. HOAc, cooled to ambient temperature, and filtered. The filtrate was washed with 6 mL of 1:1 water-methanol then 6 mL of 1:1 ether-hexanes. The off-white solid was briefly air-dried to give 46 mg (22%) of 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(3-hydroxy-4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one. Mass Spec.: 489$(M-H)^-$.

Starting from 5-amino-3-cyclopropyl-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide the following compounds were prepared by methods similiar to those used to synthesize the examples above:

Table IV



Ex. #	R^1	m.p. (°C)	MS
71	Indazol-4-yl		483
72	Indazol-5-yl	274-283	483
73	Indazol-6-yl		483
74	4-Aminophenyl		460
75	Benzoxazol-2-on-5-yl		500
76	3-Hydroxy-4-nitrophenyl	259-260	506
77	4-(*N,N*-dimethylglycinamido)phenyl	250-253	

Example 78

1-(2,4,6-Trichlorophenyl)-3-trifluoromethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 186 mg (0.50 mmol) of 5-amino-3-trifluoromethyl-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide in 6 mL of absolute ethanol was added 555 mg (3.0 mmol) of 3-methoxyphenylacetyl chloride followed by 2.26 mL (6.0 mmol) of 2.66 M sodium ethoxide in ethanol. The solution was stirred 23 h at reflux, and the heating mantle was then removed. The reaction was treated with 10 mL of 10% aq. HOAc, cooled to ambient temperature, and filtered. The filtrate was washed with 6 mL of 1:1 water-methanol then 6 mL of 1:3 ether-hexanes. The off-white solid was briefly air-dried to give 230 mg (91%) of 1-(2,4,6-trichlorophenyl)-3-trifluoromethyl-6-(3-

methoxybenzyl) pyrazolo[3,4-d]pyrimidin-4-one. Mass spec.: 503(M+H)$^+$.

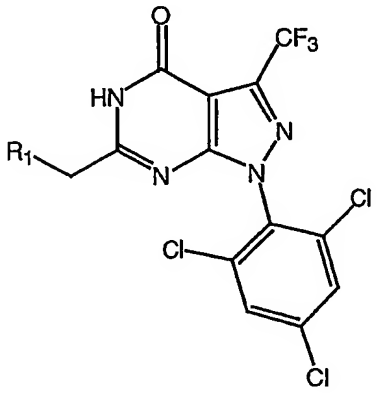
Example 79

1-(2,4,6-Trichlorophenyl)-3-trifluoromethyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 60 mg (0.12 mmol) of 1-(2,4,6-trichlorophenyl)-3-trifluoromethyl-6-(3-methoxy-4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one in 2 mL of CH_2Cl_2 was added 2 mL of a 1M solution of BBr_3 in CH_2Cl_2. The solution was stirred 2.5 h at RT and quenched with 1 N aq. HCl. The mixture was diluted with water and extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed on silica gel (elution with 1:1 hexanes-THF, then THF) to afford 1-(2,4,6-trichlorophenyl)-3-trifluoromethyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one, as an off-white solid. Mass spec.: 487(M-H)$^-$.

Starting from 5-amino-3-(trifluoromethyl)-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide the following compounds were prepared by methods similiar to those used to synthesize the compounds above:

Table V



Ex. #	R^1	m.p. (°C)	MS
80	3-aminophenyl		488
81	4-aminophenyl		488
82	4-methoxyphenyl	263-265	501
83	4-hydroxyphenyl		487
84	4-pyridyl		474
85	3-hydroxy-4-methoxyphenyl		517
86	4-hydroxy-3-methoxyphenyl		517

Example 87

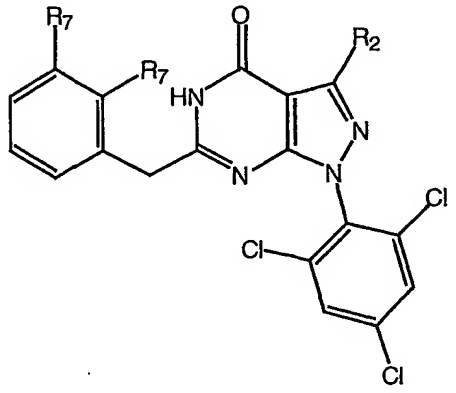
1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(3-(*N*,*N*-dimethylglycinamido)-2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one

Part A: To a stirred, cooled (0 °C) solution of 110 mg (0.23 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-amino-2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one in 4 mL of THF was added 0.084 mL (0.6 mmol) of triethylamine followed by 0.024 mL (0.3 mmol) of chloroacetyl chloride. The solution was stirred 2 h, warming to ambient temperature. The reaction was quenched by dropwise addition of 5 mL of 0.5 N aq. HCl, and the resulting solid was collected by filtration. The product was washed with water then 1:1 ether-hexanes and air-dried to afford 96 mg (76%) of 1-(2,4,6-trichloro phenyl)-3-isopropyl-6-(3-(chloroacetamido)-2-methyl benzyl)pyrazolo[3,4-d]pyrimidin-4-one, mp 237-238 °C. ^{1}H NMR (300 MHz, DMSO) δ 12.42(s, 1H); 9.69(s, 1H); 7.93(s, 2H); 7.15(d, 1H, J = 7.3 Hz); 7.07(t, 1H, J = 7.7 Hz); 6.95(d, 1H, J = 8.7 Hz); 4.25(s, 2H); 3.90(s, 2H); 3.20-3.33(m, 1H); 2.07(s, 3H); 1.30(d, 6H, J = 6.9 Hz).

Part B: To a stirred solution of of 1-(2,4,6-trichloro phenyl)-3-isopropyl-6-(3-(chloroacetamido)-2-methyl benzyl)pyrazolo[3,4-d]pyrimidin-4-one in 2 mL of THF was added 1 mL of 40% aq. dimethylamine. The solution was stirred overnight at ambient temperature and treated with

water until a precipitate formed. The precipitate was filtered, washed with water and 1:1 ether-hexanes, and air-dried to afford 46 mg (75%) of 1-(2,4,6-trichloro phenyl)-3-isopropyl-6-(3-(*N*,*N*-dimethylglycinamido)-2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one as an off-white solid, mp 219-222 °C. Mass spec.(ESI-): 561((M-H)$^-$). By allowing *m*-substituted anilines to react with suitable acylating agents and performing further synthetic manipulations as necessary, the following compounds wherein R^1 = phenyl were prepared by methods similiar to those used to synthesize the compounds above:

Table VI



Ex. #	R^2	R^7(meta)	R^7(ortho)	mp(°C)	MS
88	Et	CH_3SO_2NH	H		524
89	*i*-Pr	CH_3SO_2NH	H		538
90	*i*-Pr	CF_2HCONH	H		538
91	*i*-Pr	CH_3CONH	H		502
92	*i*-Pr	$CH_3NHCONH$	H		517
93	*i*-Pr	$HOCH_2CH_2NHCONH$	H		547
94	*i*-Pr	$HO(CH_2)_4NHCONH$	H		577
95	*i*-Pr	(Fluorophen-4-yl)$CH_2NHCONH$	H		613
96	*i*-Pr	(Fluorophen-3-yl)$CH_2NHCONH$	H		613
97	*i*-Pr	Morpholin-4-ylCONH	H		575
98	*i*-Pr	$PhCH_2N(CH_3)CONH$	H		609
99	*i*-Pr	Tetrahydrofur-2-yl$CH_2NHCONH$	H		585

100	*i*-Pr	4-hydroxypiperid-1-ylCONH	H		589
101	*i*-Pr	Pyrid-2-ylCH$_2$NHCONH	H		596
102	*i*-Pr	Pyrid-3-ylCH$_2$NHCONH	H		596
103	*i*-Pr	4-Methylpiperazin-1-ylNHCONH	H		603
104	*i*-Pr	Pyrid-3-ylNHCONH	H		582
105	*i*-Pr	(CH$_3$)$_2$NCH$_2$CH$_2$N(CH$_3$)CONH	H		590
106	Et	(CH$_3$)$_2$NCH$_2$CONH	Me	218-221	547
107	*i*-Pr	(Methoxyphen-2-yl)CH$_2$NHCONH	H		625
108	*i*-Pr	(Methoxyphen-4-yl)CH$_2$NHCONH	H		625
109	*i*-Pr	2-hydroxypiperid-1-ylCONH	H		589
110	Et	CH$_3$CONH	H		488

Example 111

1-(2,4,6-Trichlorophenyl)-3-ethyl-6-(4-methanesulfonylaminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 45 mg (0.1 mmol) of 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one in 2 mL of ether-CH_2Cl_2 was added 0.5 mL of pyridine followed by 0.020 mL (0.26 mmol) of methanesulfonyl chloride. The solution was stirred 39 h at ambient temperature and poured into 1 N aq. HCl. The mixture was extracted with EtOAc, then hexanes. The combined organic extracts were washed with water then brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford 52 mg of 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-methanesulfonyl aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one as an amorphous solid. Mass spec.(ESI+): 526$(M+H)^+$.

Example 112

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(piperazin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

Part A: To a stirred, cooled (0 °C) solution of 9.26 g (20 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one in 45 mL of THF and 10 mL of DMF was added 3.90 mL (28 mmol) of triethylamine followed by 1.99 mL (25 mmol) of chloroacetyl chloride over 5 min. The solution was stirred 30 min. at 0 °C and quenched by addition of 150 mL of 0.1 N aq. HCl. The resulting solid was collected by filtration, washed with water then 1:1 ether-hexanes, and air-dried to afford 10.2 g (95%) of 1-(2,4,6-trichloro phenyl)-3-isopropyl-6-(4-(chloroacetamido)benzyl)pyrazolo [3,4-d]pyrimidin-4-one as a white solid. ^1H NMR (300 MHz, DMSO) δ 12.49(s, 1H); 9.74(s, 1H); 7.97(s, 2H); 7.46(d, 2H, J = 8.0 Hz); 7.20(d, 2H, J = 8.8 Hz); 4.19(s, 2H); 3.80(s, 2H); 3.20-3.33(m, 1H); 1.28(d, 6H, J = 6.9 Hz).

Part B: To a stirred solution of 300 mg (0.55 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(chloro acetamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one in 6 mL of 1:1 DMF-THF was added 1 g of piperazine. The solution was stirred overnight at ambient temperature and poured into water. The mixture was extracted twice with EtOAc, and the combined organic extracts were washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to afford 230 mg (71%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(piperazin-1-ylmethylcarbonylamino) benzyl)pyrazolo[3,4-d]pyrimidin-4-one as an off-white solid. Mass spec.(ESI+): 588($(M+H)^+$).

Example 113

(*S*)-1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(*N*-*t*-butoxycarbonylprolinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 105 mg (0.22 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo [3,4-d]pyrimidin-4-one and 235 mg (1.09 mmol) of Boc-L-proline in 2 mL of DMF was added 0.35 mL (2.5 mmol) of triethylamine followed by 490 mg (1.11 mmol) of Bop. The solution was stirred overnight at ambient temperature then poured into EtOAc. This solution was washed sequentally with 0.5 M HCl then dilute aq. Na_2CO_3 then brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was recrystallized from EtOAc-hexanes to afford 116 mg (80%) of (*S*)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-*t*-butoxycarbonyl prolinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one as a white solid, mp 225-226 °C, Mass spec.: 657 $M-H^-$).

Example 114

(*S*)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(prolinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

Fifty mg (0.076 mmol) of (S)-1-(2,4,6-trichloro phenyl)-3-isopropyl-6-(4-(*N*-*t*-butoxycarbonylprolinamido)benzyl) pyrazolo[3,4-d]pyrimidin-4-one was dissolved in 2 mL of 4 M HCl, and the solution was stirred 1 h at RT. The solution was concentrated under reduced pressure to afford 45 mg (100%) of (*S*)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(prolinamido)benzyl) pyrazolo[3,4-d]pyrimidin-4-one as a white, amorphous solid. ^{1}H NMR (300 MHz, DMSO) δ 12.42(s, 1H); 10.67(s, 1H); 7.97(s, 2H); 7.49(d, 2H, J = 8.5 Hz); 7.23(d, 2H, J = 8.4 Hz); 4.27-4.31(m, 1H); 3.82(s, 2H); 3.18-3.34(m, 5H); 2.28-2.40(m, 1H); 1.84-1.95(m, 3H); 1.28(d, 6H, J = 6.9 Hz).

Example 115

1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(dimethylamino methyl)-3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 464 mg (1.0 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-hydroxybenzyl)pyrazolo [3,4-d]pyrimidin-4-one in 10 mL of glacial HOAc was added 0.4 mL of 37% aq. formaldehyde followed by 0.5 mL of 40% aq. dimethylamine. The solution was stirred overnight at RT, and it was then heated to just below reflux for 20 min. The solution was poured into water and extracted with EtOAc. The organic extract was washed (brine), dried ($MgSO_4$), and chromatographed on silica gel (elution with EtOAc) to afford, after removal of solvent, 135 mg (26%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(dimethylaminomethyl)3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one as an off-white, amorphous solid. Mass spec.(ESI+): 520$(M+H)^+$.

Example 116

1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-pyridylmethyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 167 mg (0.5 mmol) of 1-(2,4,6-trichlorophenyl)-3-ethyl-4-carboxamido-5-aminopyrazole in 5 mL of ethanol was added 480 mg (3.0 mmol) of ethyl 3-pyridyl acetate followed by 1.13 mL (3.0 mmol) of 2.66 M NaOEt in ethanol. The solution was stirred overnight at reflux, and the product was precipitated by treatment with 10 mL of 10% aq. HOAc. The mixture was filtered, and the product was washed with 1:1 MeOH-water then 1:1 ether-hexanes and air dried to afford 210 mg (97%) of 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-pyridylmethyl) pyrazolo[3,4-d]pyrimidin-4-one as an off-white solid, mp 257-260 °C. ^{1}H NMR (300 MHz, DMSO) δ 12.56(s, <1H (exchanges with solvent)); 8.46(d, 1H, J = 1.5); 8.40(dd, 1H, J = 4.8, 1.5 Hz); 7.96(s, 2H); 7.60-7.64(m, 1H); 7.25-7.30(m, 1H); 3.90(s, 2H); 2.83(q, 2H, J = 7.3Hz); 1.23(t, 3H, J = 7.5 Hz).

Example 117

(+/-)-1-(2,4,6-Trichlorophenyl)-3-ethyl-6-(α-hydroxy benzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 167 mg (0.50 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-4-carboxamido-5-amino pyrazole in 6 mL of ethanol was added 544 mg (3.0 mmol) of (+/-) ethyl mandelate followed by 1.13 mL (3.0 mmol) of 2.66 M NaOEt in ethanol. The solution was stirred overnight at reflux, and the product was precipitated by treatment with 10 mL of 10% aq. HOAc. The mixture was filtered, and the product was washed with 1:1 MeOH-water then 1:1 ether-hexanes and air dried to afford 210 mg (94%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(α-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one as an off-white solid, mp 246-248 °C. Mass spec.(ESI-): 449(M-H)$^-$.

Example 118

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(ethenesulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred, cooled (0 °C) solution of 231 mg (0.5 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one and 0.14 mL (1.0 mmol) of Et_3N in 4 mL of THF was added 0.063 mL (0.6 mmol) of 2-chloroethanesulfonyl chloride. The solution was stirred 1 h, warming to ambient temperature. The solution was poured into 10% aq. citric acid and extracted with EtOAc. The organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed (elution with 1:1 EtOAc-hexanes) to afford 221 mg (80%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(ethenesulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one as an off-white solid. ^1H NMR (300 MHz, DMSO) δ 12.47(br. s, 1H); 9.92(br. s, 1H); 7.97(s, 2H); 7.17(d, 2H, J = 8.4 Hz); 7.02(d, 2H, J = 8.4 Hz); 6.69(dd, 1H, J = 16.5, 9.9Hz); 6.04(d, 1H, J = 16.5 Hz); 5.96(d, 1H, J = 9.9 Hz); 3.78(s, 2H); 3.18-3.32(m, 1H); 1.28(d, 6H, J = 7.0 Hz).

Example 119

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethanesulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred, solution of 23 mg(0.042 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(ethenesulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one in 1 mL of THF was added 1 mL of 2M diethylamine in THF. The solution was stirred 3 h and concentrated under reduced pressure. The product was dissolved in 1 mL of benzene and 0.05 mL of MeOH, frozen, and lyophilized to afford 25 mg (100%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethenesulfonamido) benzyl)pyrazolo[3,4-d]pyrimidin-4-one as an amorphous white solid. ^1H NMR (300 MHz, DMSO) δ 7.96(s, 2H); 7.19(d, 2H, J = 8.5 Hz);

7.08(d, 2H, J = 8.8 Hz); 3.79(s, 2H); 3.18-3.32(m, 1H); 3.13(t, 2H, J = 7.5 Hz); 2.53(t, 2H, J = 7.5Hz); 1.99(s, 6H); 1.28(d, 6H, J = 7.0 Hz).

Example 120

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(hydroxymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 347 mg (1.0 mmol) of 5-amino-3-isopropyl-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide in 6 mL of absolute ethanol was added 777 mg (4.0 mmol) of ethyl 4-(hydroxymethyl)phenylacetate followed by 2.0 mL (5.33 mmol) of 2.66 M sodium ethoxide in ethanol. The solution was stirred 18 h at reflux, and the heating mantle was then removed. The reaction was treated with 25 mL of 5% aq. HOAc, cooled to ambient temperature, and extracted with EtOAc. The organic extract was washed twice with water and once with brine, dried ($MgSO_4$), and chromatographed on silica gel (elution with 1:1 EtOAc-hexanes) to give, after removal of solvent, 320 mg (67%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(hydroxy methyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one as a white, amorphous solid. ^1H NMR (300 MHz, $CDCl_3$) d 11.46(br. s, 1H); 7.54(s, 2H); 7.42(d, 2H, J = 8.1 Hz); 7.31(d, 2H, J = 8.5 Hz); 4.66(s, 2H); 4.00(s, 2H); 3.47(septet, 1H, J = 7.0 Hz); 1.48(d, 6H, J = 7.0 Hz).

Example 121

(+/-)-1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(1,4-dimethylpiperazine-2-ylcarboxamido)benzyl) pyrazolo[3,4-d]pyrimidin-4-one

Part A: To a stirred, cooled (0 °C) solution of 463 mg (1.0 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one and 0.28 mL (2.0 mmol) of Et_3N in 8 mL of THF was added 0.131 mL (1.2 mmol) of 2,3-dichloropropanoyl chloride. The solution was stirred 0.5 h, warming to ambient temperature. The solution was quenched with water and filtered. The solid

was washed with 0.1 N aq. HCl, then water, then 1:1 hexanes-ether. The product was air-dried briefly to afford 390 mg (71%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-chloroacrylamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one as an amorphous solid. ^{1}H NMR (300 MHz, DMSO) δ 12.49(br. s, 1H); 10.14(br. s, 1H); 7.97(s, 2H); 7.53(d, 2H, J = 8.4 Hz); 7.22(d, 2H, J = 8.4 Hz); 6.36(d, 1H, J = 2.6 Hz); 6.03(d, 1H, J = 2.5 Hz); 3.82(s, 2H); 3.18-3.32(m, 1H); 1.28(d, 6H, J = 7.0 Hz).

Part B: To a stirred, solution of 112 mg (0.2 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-chloroacryl amido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one in 2 mL of THF was added 0.5 mL of *N, N'*-dimethylethylene diamine. The solution was stirred overnight, poured into water, and extracted with EtOAc. The organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to afford 102mg (84%) of 1-(2,4,6-trichloro phenyl)-3-isopropyl-6-(4-(1,4-dimethyl piperazine-2-ylcarboxamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one as an amorphous white solid. Mass spec.(ESI+): 602.1608$(M+H)^+$.

Example 122

1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(carbethoxymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

The amino carboxamide, 5-amino-3-isopropyl-1-(2,6-dichlorophenyl)pyrazole-4-carboxamide (0.30 g, 0.96 mmol), *p*-diethyl phenylenediacetate (8 eq, 1.92 g, 7.66 mmol) and sodium ethoxide (21% in ethanol, 8 eq, 2.90 mL, 7.66 mmol) were refluxed overnight in ethanol (20 mL). The reaction was cooled and 10% aq HOAc was added. The mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$ and evaporated to dryness. The oily solid was purified by silica gel column chromotography with 1:1hexane/ether as the eluent. The product, 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(carbethoxymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

(0.44 g, 93 % yield), was recovered as a white solid, mp 168-169 °C. Mass Spec.: 499 $(M+H)^+$.

Example 123

1-(2,6-Dichlorophenyl)-3-isopropyl-6-(4-(carboxymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

The ester, 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(carbethoxymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one (1.20 g, 2.4 mmol) was stirred at RT overnight with THF (50 mL), water (15 mL) and 1 N lithium hydroxide (7.20 mL). The solution was evaporated to near dryness, diluted with 1 N hydrochloric acid, vigorously stirred and the solid was collected by filtration and dried under high vacuum to give 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-carboxymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one (1.01 g, 89 % yield) as a white solid, mp 212-214 °C. Mass Spec.: 471 $(M+H)^+$.

Example 124

1-(2,6-Dichlorophenyl)-3-isopropyl-6-(4-(2-(*N*,*N*-dimethyl amino)ethylaminocarbonylmethyl)benzyl) pyrazolo[3,4-d]pyrimidin-4-one

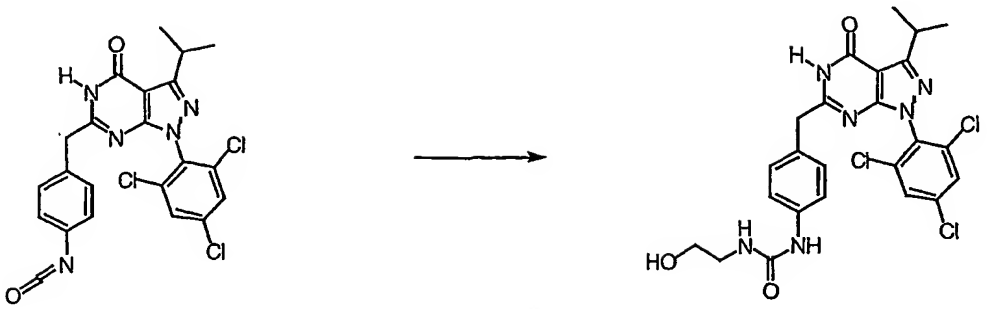
The acid, 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-carboxymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one (0.100 g, 0.21 mmol) and *N*,*N*-dimethyethylenediamine (5 eq, 0.12 mL, 1.06 mmol) were suspended in DMF (3 mL). DIEA (5 eq, 0.18 mL, 1.06 mmol) was added and the suspension was stirred at RT for ten minutes. BOP (1.5 eq, 0.141 g, 0.32 mmol) was added and the reaction was stirred at RT overnight. The suspension was diluted with water, extracted with EtOAc, washed with water and brine, dried over $MgSO_4$ and evaporated to dryness. The oily residue was crystallized from a mixture of EtOAc, hexane and ether to give 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(2-(*N*,*N*-dimethylamino)ethylaminocarbonylmethyl)benzyl) pyrazolo[3,4-d]pyrimidin-4-one (0.039 g, 34 % yield) as a white solid, mp 170-172 °C. Mass Spec.: 541 $(M+H)^+$.

Example 125

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(2-(morpholine-4-yl)ethylaminocarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one

A flask equipped with a reflux condensor was flame-dried *in vacuo* and a nitrogen atmosphere was introduced. The flask was charged with triphosgene (1.37 g, 4.62 mmol). The reagent was dissolved in dry 1,2-dichloroethane (25 mL), and triethylamine (0.64 mL, 4.62 mmol) was added. The reaction was cooled to -30 °C, and 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo [3,4-d]pyrimidin-4-one (1.1 g, 2.38 mmol) was added. Stirring was continued for 10 minutes and the reaction was the warmed to reflux. After heating for one hour, the reaction was cooled, diluted with methylene chloride, and washed sequentially with water and brine. The organic phase was dried over magnesium sulfate, filtered and evaporated to give the isocyanate (1.2 g). This material was of sufficient quality for the subsequent transformations.

The isocyanate (75.5 mg, 0.155 mmol) was dissolved in dry methylene chloride (2.0 mL) under a nitrogen atmosphere. 4-(2-aminoethyl)morpholine (30 μΛ, 0.232 mmol) was added, and stirring was continued for 1 hour. The precipitate was filtered and rinsed with three portions of methylene chloride and dried *in vacuo* to give 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(morphline-4-yl)ethylaminocarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one (68 mg, 0.110 mmol, 71%). Mass spec. (ESI+) 618 $(M+H)^+$.



Example 126

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(2-hydroxyethylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one

Alternatively, the ureas may be prepared by the following procedure, which is suitable for parallel synthesis. The isocyanate (74 mg, 0.152 mmol) was dissolved in dry methylene chloride (3.0 mL) under a nitrogen atmosphere. Ethanolamine (14 μΛ, 0.227 mmol) was added and stirring continued for 15 minutes. Methanol (1.0 mL) was added to generate a homogeneous solution. The acidic ion exchange resin AG 50W-X8 (158 mg) was added. The reaction was then filtered and the solvents removed by evaporation. The product 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-hydroxyethyl aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one was obtained in excellent yield (78 mg, 93%). Mass spec. (ESI-) 547 $(M-H)^-$.

Example 127

1-(2-Chloro-6-methylphenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one

Part A: To a stirred suspension of 14.2 g (100 mmol) of 2-chloro-6-methylaniline in 40 mL conc. HCl at 0 °C was added a solution of 6.9 g (100 mmol) of sodium nitrite in 40 mL water dropwise via addition funnel. After stirring one hour at 0 °C a solution of 67.6 g (300 mmol) tin (II) chloride dihydrate in 70 mL conc. HCl was added dropwise

via addition funnel. The reaction was sealed and placed in the refrigerator for 24 h. The mixture was filtered and the solid was washed with brine and then petroleum ether. The solid was taken up in 250 mL of 2 N NaOH, stirred 10 min. and filtered. This solid was dissolved in 100 mL diethyl ether and acidified with 4N HCl in dioxane. The solid was collected by suction filtration, washed with diethyl ether and dried to afford 10.25 g (53%) of 2-chloro-6-methylhydrazine hydrochloride, mp 220-222 (dec)°C. Mass Spec (CI+): 157 $(M+H)^+$.

Part B: To a stirred suspension of 3.0 g (15.5 mmol) of 2-chloro-6-methylhydrazine hydrochloride in 20 mL ethanol was added 2.2 mL (15.5 mmol) of triethylamine followed after 10 min by 1.5 mL (16.5 mmol) of isobutyraldehyde. The solution was stirred at room temperature for 2 h, poured into water and extracted with diethyl ether. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 2.95 g (90%) of the imine intermediate as a liquid. The imine was taken up in 15 mL dimethylformamide, cooled to 0 °C, and 2.99 g (16.8 mmol) of *N*-bromosuccinimide was added in small portions. After stirring at 0 °C for 30 min the reaction was diluted with diethyl ether and water. The layers were separated and the aqueous phase with extracted with diethyl ether. The organic extracts were combined, washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the bromohydrazone intermediate.

To a stirred solution of the bromohydrazone in 25 mL ethanol was added an ice cold solution of the anion of malononitrile prepared by adding 10.4 mL (28 mmol) of sodium ethoxide to 1.82 g (28 mmol) of malononitrile in 25 mL ethanol at 0 °C. The mixture was heated to reflux for 30 min and then concentrated to one third the volume under reduced pressure. This solution was treated with 10% glacial acetic acid, diluted with water, and

extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography on silica gel using 2:1 hexanes-EtOAc as eluant afforded 1.82 g (47%) of 5-amino-4-cyano-3-isopropyl-1-(2-chloro-6-methylphenyl)pyrazole, mp 116-118 °C. Mass Spec. (CI+): 275 $(M+H)^+$.

Part C: A mixture of 1.5 g (5.5 mmol) of 5-amino-4-cyano-3-isopropyl-1-(2-chloro-6-methylphenyl)pyrazole in 5 mL conc. H_2SO_4 was stirred at room temperature for 24 hours. The reaction was slowly quenched with ice and then diluted with water. The solution was made basic with saturated Na_2CO_3, stirred 2 h and filtered. The solid was recrystallized from hexanes/EtOAc to afford 847 mg (53%) of 5-amino-3-isopropyl-1-(2-chloro-6-methylphenyl) pyrazole-4-carboxamide, mp 72-74 °C. Mass Spec. (ES-): 291 $(M-H)^-$.

Part D: To a stirred solution of 1.4 g (4.8 mmol) 5-amino-3-isopropyl-1-(2-chloro-6-methyl-phenyl)pyrazole-4-carboxamide in 100 mL absolute ethanol was added 5.14 g (28.8 mmol) of 4-amino-phenylacetate followed by 10.7 mL (28.8 mmol) of 2.66 M sodium ethoxide in ethanol. The solution was stirred 18 h at reflux and the heating mantle was then removed. The reaction was treated with water and 10% aq. HOAc, cooled to ambient temperature, and filtered. The solid purified by coloumn chromatography on silica gel using 1:1 hexanes-EtOAc as eluant to afford 743 mg (38%) of 1-(2-chloro-6-methyl phenyl)-3-isopropyl-6-(4-aminobenzyl)-pyrazolo[3,4-d]pyrimidin-4-one, mp 206-207 °C. Mass Spec.(CI+): 408 $(M+H)^+$.

Example 128

1-(2-Chloro-6-methylphenyl)-3-isopropyl-6-(4-(N,N-dimethylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one hydrochloride salt

To a stirred solution of 500 mg (1.22 mmol) of 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-aminobenzyl)-pyrazolo[3,4-d]pyrimidin-4-one in 10 mL dry CH_2Cl_2 was added 0.85 mL (6.1 mmol) triethylamine followed by 632 mg (6.1 mmol) N,N-dimethylglycine and then 1.17 g (6.1 mmol) of 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). The reaction was stirred for 18 h at ambient temperature and then transferred directly to a flash column of silica gel and eluted with 5% MeOH in CH_2Cl_2. The isolated solid was dissolved in 20 mL dioxane and 1.1 mL of 4 N HCl in dioxane was added. The solid was collected by suction filtration and dried to give 490 mg (76%) of 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-(N,N-dimethylglycinamido)benzyl)pyrazolo [3,4-d]pyrimidin-4-one hydrochloride salt, mp 297-299 °C.

Example 129

1-(2,6-Dichloro-4-methylcarboxamido phenyl)-3-ethyl-6-(4-methoxybenzyl)pyrazolo[3,4-d] pyrimidin-4-one

Part A: To a stirred suspension of 4.33 g (18.5 mmol) of ethyl 4-amino-3,5-dichlorobenzoate in 8 mL conc. HCl at 0 °C was added a solution of 1.28 g (18.5 mmol) of sodium nitrite in 8 mL water dropwise. After stirring at 0 °C for 45 min, a solution of 12.52 g (55.5 mmol) tin(II) chloride in 14 mL conc. HCl was added dropwise. The reaction was sealed and placed in the refrigerator for 18 h. The solid was collected by suction filtration, washed with brine and then 2:1 petroleum ether-diethyl ether, treated with 1 N NaOH, and filtered. This solid was dissolved in diethyl ether, acidified with 4 N HCl in dioxane, filtered and washed with diethyl ether to give 2.85 g (54%) of ethyl 3,5-dichloro-4-hydrazinobenzoate

hydrochloride, mp 225-227 (dec)°C. Mass Spec.: (CI+) 249 (M+).

Part B: A mixture of 2.5 g (8.75 mmol) ethyl 3,5-dichloro-4-hydrazinobenzoate hydrochloride, 1.1 g (7.3 mmol) 1-(ethoxypropylidine)malononitrile and 1.22 mL (8.75 mmol) triethylamine in 100 mL of ethanol was stirred at reflux for 66 h. The reaction was taken to one-third the volume via rotary evaportation under reduced pressure and the remaining solution was treated with water, stirred 30 min and filtered. Recrystallization from hexanes/EtOAc gave 1.16 g (45%) of 5-amino-4-cyano-3-ethyl-1-(2,6-dichloro-4-carboethoxy phenyl)pyrazole, mp 173-175 °C. Mass Spec.: (CI+) 353 (M+).

Part C: A solution of 1.64 g (4.64 mmol) of 5-amino-4-cyano-3-ethyl-1-(2,6-dichloro-4-carboethoxyphenyl)-pyrazole in 8 mL conc. H_2SO_4 was stirred at room temperature for 4 hours. The reaction was quenched carefully with ice and diluted with water. The solid was collected by suction filtration, washed with water and dried to give 1.26 g (73%) of 5-amino-3-ethyl-1-(2,6-dichloro-4-carboethoxyphenyl)pyrazole-4-carboxamide, mp 194-196 °C. Mass Spec.: (CI+) 371 (M+).

Part D: To a stirred solution of 500 mg (1.35 mmol) of 5-amino-3-ethyl-1-(2,6-dichloro-4-carboethoxyphenyl) pyrazole-4-carboxamide in 10 mL ethanol was added 1.45 g (8.1 mmol) of methyl 4-methoxyphenylacetate followed by 2.6 mL (8.1 mmol) of 2.66 M sodium ehtoxide in ethanol. The reaction was heated at relux for 18 h and then 10% aq. HOAc was added. After stirring an additional hour at relux, the heat was removed and the reaction solution was poured into ice water, stirred 10 min. and filtered. The solid was washed with water and diethyl ether and dried to give 480 mg (75%) of 1-(2,6-dichloro-4-carboxyphenyl)-

3-ethyl-6-(4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one, mp 277 °C. Mass Spec.: (ES-) 471 $(M-H)^-$.

Part E: To a stirred solution of 100 mg (0.21 mmol) of 1-(2,6-dichloro-4-carboxyphenyl)-3-ethyl-6-(4-methoxy benzyl)pyrazolo[3,4-d]pyrimidin-4-one was added 0.3 mL (2.1 mmol) of triethylamine followed by 71 mg (1.05 mmol) of methylamine hydrochloride and then 202 mg (1.05 mmol) of EDC. The reaction was stirred at ambient temperature for 18 h, transferred directly to a flash column of silica gel and eluted with 5% MeOH in CH_2Cl_2 to give 14 mg (14%) of 1-(2,6-dichloro-4-(methylcarboxamido) phenyl)-3-ethyl-6-(4-methoxybenzyl)pyrazolo[3,4-d] pyrimidin-4-one, mp 280-282 °C. Mass Spec.: (CI+) 486 (M+).

Example 130

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(*t*-butoxycarbonylaminosulfonamido)benzyl)pyrazolo [3,4-d]pyrimidin-4-one

To a stirred, cooled solution of 0.11 mL (1.26 mmol) of chlorosulfonyl isocyanate in 5 mL of CH_2Cl_2 was added 0.13 mL of *t*-BuOH. The solution was stirred 10 min. and added to a stirred, cooled (0 °C) solution of 231 mg (0.5 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one and 0.2 mL (1.4 mmol) of Et_3N in 5 mL of CH_2Cl_2. The solution was stirred 1 h warming to ambient temperature, and it was then poured into 1 N aq. HCl. The mixture was extracted with EtOAc, and the organic extract was washed (brine), dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed on silica gel (elution with 1:1 EtOAc-hexanes, then EtOAc) to afford 250 mg (78%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*t*-butoxycarbonyl aminosulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one as a white solid. ^1H NMR (300 MHz, DMSO) δ 12.44(s, 1H); 11.12(br. s, 1H); 9.70(br. s, 1H); 7.97(s, 2H); 7.21(d,

2H, J = 8.4 Hz); 7.02(d, 2H, J = 8.4 Hz); 3.78(s, 2H); 3.19-3.30(m, 1H); 1.27(d, 6H, J = 6.9 Hz); 1.21(s, 9H).

Example 131

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(3-aminoindazol-5-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred solution of 139 mg (0.40 mmol) of 5-amino-3-isopropyl-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxamide in 3 mL of absolute ethanol was added 329 mg (1.50 mmol) of ethyl 3-aminoindazol-5-ylacetate followed by 1.13 mL (3.0 mmol) of 2.66 M sodium ethoxide in ethanol. The solution was stirred 16 h at reflux, and the heating mantle was then removed. The reaction was treated with 8 mL of 10% aq. HOAc, poured into water, and extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed on silica gel (gradient elution with 5% to 10% MeOH-CH_2Cl_2) to give, after removal of solvent, 123 mg (61%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-aminoindazol-5-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one as a white, amorphous solid. Mass spec. 502.0712$(M + H)^+$.

Example 132

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(benzoxazol-2-on-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one

To a stirred, cooled (0 °C) solution of 309 mg (0.063 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-amino-3-hydroxybenz)pyrazolo[3,4-d]pyrimidin-4-one in 1 mL of THF was added 0.13 mL (1.0 mmol) of triethylamine followed by 0.05 mL (0.095 mmol) of 1.93 M phosgene in toluene. The solution was stirred 15 min., treated with 4 mL of 0.1 N aq. NaOH, and stirred 64 h at RT. The reaction was poured into 1 N aq. HCl and extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$ plus activated charcoal and celite), and concentrated under reduced pressure to afford 26 mg (81%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(benzoxazol-2-on-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one as an

amorphous solid. ^{1}H NMR (300 MHz, DMSO) δ 12.48(s, 1H); 11.57(br. s, 1H); 7.98(s, 2H); 7.03(dd, 1H, J = 8.1, 1.4 Hz); 6.97(d, 1H, J = 8.1 Hz); 3.84(s, 2H); 3.19-3.30(m, 1H); 1.28(d, 6H, J = 7.0 Hz).

Example 133

1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethoxycarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one

To a stirred, cooled(-78 °C) solution of 0.10 mL(1.0 mmol) of N,N-dimethylethanolamine in 1 mL of THF was added 0.56 mL(0.90 mmol) of 1.6 M *n*-BuLi in hexanes over 2 min. The solution was stirred 5 min. at -78 °C and treated with 49 mg (0.10 mmol) of the isocyanate prepared in Example 107 above. The mixture was stirred 10 min., becoming homogeneous as it warmed to 0 °C. The reaction was diluted with 5% aq. HOAc, then made slightly basic with saturated aq. $NaHCO_3$. The mixture was extracted with EtOAc, and the organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to afford 43 mg(74%) of 1-(2,4,6-Trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethoxycarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one as a white solid, mp. 218-220 °C. Mass spec: 577$(M + H)^+$.

Example 134

1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(1-methylpyrroy-2-ylmethyl)pyrazolo [3,4-d]pyrimidin-4-one

To a stirred solution of 1.74 g (5.0 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-4-carboxamido-5-amino-pyrazole in 30 mL of ethanol was added 2.9 mL (20 mmol) of methyl 1-methyl-2-pyrroleacetate followed by 7.50 mL (20 mmol) of 2.66 M NaOEt in ethanol. The solution was stirred overnight at reflux, and the product was precipitated by treatment with 40 mL of 10% aq. HOAc. The mixture was filtered, and the product was washed with 1:1 MeOH-water then 1:1 ether-hexanes and air dried to

afford 2.07 g (92%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(1-methylpyrroy-2-ylmethyl)pyrazolo [3,4-d]pyrimidin-4-one as an off-white solid, mp 219-221 °C. Mass spec.(ESI+): 450(M+H)$^+$.

Example 135

1-(3-Formyl-2,4,6-trichlorophenyl)-3-isopropyl-6-(1-methylpyrroy-2-ylmethyl)pyrazolo [3,4-d]pyrimidin-4-one

To a stirred, cooled(-60 °C) solution of 902 mg (2.0 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(1-methyl pyrroy-2-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one in 10 mL of THF was added 2.56 mL (4.1 mmol) of 1.6 M *n*-BuLi in hexanes over 2 min. The solution was stirred 10 min. at -60 °C and treated with 1 mL DMF. The reaction solidified and was broken up by stirring, shaking, and warming to ambient temperature. The reaction was quenched with deuteromethanol then aq. HOAc. The mixture was extracted with EtOAc, and the organic extraxt was washed (brine), dried (MgSO4), and concentrated under reduced pressure. The crude product was re-crystallized from EtOAc-hexanes to afford 560 mg(60%) of 1-(3-formyl-2,4,6-trichloro phenyl)-3-isopropyl-6-(1-methylpyrroy-2-ylmethyl)pyrazolo [3,4-d]pyrimidin-4-one as an orange solid. Mass spec.(ESI-): 450(M-H)$^-$.

Example 136

1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylaminocarbonyl)benzyl)pyrazolo [3,4-d]pyrimidin-4-one

Part A: To a stirred solution of 7.5 g(153 mmol) sodium cyanide in 75 mL of THF was added 40 mL of DMF followed by 11.5 g(50.2 mmol) of of methyl 4-(bromomethyl)benzoate in 30 mL of DMF over 10 min. The solution was stirred 18 and treated with 100 mL water. The mixture was filtered, rinsed with water, and air-dried briefly to give 6.7 g (76%) of 4-(carbomethoxy)phenylacetonitrile as a white

solid. ^{1}H NMR (300 MHz, DMSO) δ 7.95(d, 2H, J = 8.4 Hz); 7.47(d, 2H, J = 8.5 Hz); 4.14(s, 2H); 3.82(s, 3H).

Part B: The above nitrile ester was stirred with 120 mL of 6 N aq. HCl for 18 h at reflux and then cooled. The mixture was diluted with 160 mL water and then filtered. The white solid was rinsed with water, air-dried briefly, and placed in a vacuum oven at 75 °C for 1h. This affords 6.89 g (100%) of 4-(carboxy)phenylacetic acid. ^{1}H NMR (300 MHz, DMSO) δ 7.92(d, 2H, J = 8.5 Hz); 7.49(d, 2H, J = 8.4 Hz); 3.63(s, 2H).

Part C: To a stirred solution of 2.0 g (11.1 mmol) of 4-(carboxy)phenylacetic acid in 28 mL of absolute ethanol was added 0.5 mL of conc. Sulfuric acid. The solution was stirred 2 h at reflux and then cooled. The reaction was made basic with sodium carbonate and extracted with ether. The organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to afford 2.3 g (88%) of ethyl 4-(carbethoxy)phenylacetate as an oil. ^{1}H NMR (300 MHz, CDCl3) δ 8.01(d, 2H, J = 8.4 Hz); 7.36(d, 2H, J = 8.1 Hz); 4.37(q, 2H, J = 7.1 Hz); 4.16(q, 2H, J = 7.2 Hz); 1.39(t, 3H, J = 7.2 Hz); 1.25(t, 3H, J = 7.2 Hz).

Part D: To a stirred solution of 174 mg (0.50 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-4-carboxamido-5-aminopyrazole in 6 mL of ethanol was added 473 mg (2.0 mmol) of ethyl 4-(carbethoxy)phenylacetate followed by 0.94 mL (2.5 mmol) of 2.66 M NaOEt in ethanol. The solution was stirred overnight at reflux, and the product was precipitated by treatment with 8 mL of 10% aq. HOAc then 2 mL of saturated aq. $NaHCO_3$. The mixture was filtered, and the product was washed with 1:1 MeOH-water then 1:1 ether-hexanes and air dried to afford 232 mg (89%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-

(carbethoxy)benzyl)pyrazolo [3,4-d]pyrimidin-4-one as an off-white solid, mp 233-235 °C. Mass spec.(ESI+): 519.0754 $(M+H)^+$.

Part E: To a stirred solution of 130 mg (0.250 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(carbethoxy) benzyl)pyrazolo[3,4-d]pyrimidin-4-one in 2 mL of THF was added 42 mg (1.0 mmol) of lithium hydroxide hydrate in 2 mL of water followed by 0.25 mL of methanol. The solution was stirred 3.5 h at RT and 10 min. at reflux. The reaction was diluted with ether, and washed twice with 0.1 N aq. NaOH. The combined aq. washings were acidified, and the resulting mixture was extracted with chloroform, then EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford 123 mg (100%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(carboxy)benzyl)pyrazolo[3,4-d]pyrimidin-4-on as a white solid, mp. 294-295 °C.

Part F: To a stirred solution of 49 mg (0.10 mmol) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(carboxy)benzyl) pyrazolo[3,4-d]pyrimidin-4-one and 0.06 mL(0.5 mmol) of 1-amino-4-methylpiperazine in 1 mL of DMF was added 0.052 mL of DIEA followed by 48 mg (0.15 mmol) of TBTU. The solution was stirred 16 h at 45 °C, cooled to RT, and poured into water. The mixture was extracted with EtOAc, and the organic extract was concentrated under reduced pressure. Chromatography with 4:1 chloroform-MeOH afforded 34 mg (58%) of 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylaminocarbonyl) benzyl)pyrazolo[3,4-d]pyrimidin-4-on as a white solid. Mass spec: (ESI+) 588$(M + H)^+$.

Example 137

1-(4-(acetamidophenyl-3-yl)-2, 6-dichlorophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo [3,4-d]pyrimidin-4-one

A solution of 1-(4-bromo-2, 6-dichlorophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one (200 mg, 0.383 mmol) and 3-acetamidobenzeneboronic acid (82 mg, 0.458 mmol) in a 25% solution of ethanol in toluene was stirred at RT under nitrogen for 30 min. Sodium carbonate solution (0.38 mL of a 2N solution, 0.766 mmol) was added followed by tetrabutylammonium bromide (6.1 mg, 0.019 mmol) and tetrakis(triphenylphosphine) palladium(0) (2 mg, catalytic). The reaction was stirred at reflux overnight, cooled to RT, filtered through Celite, washed with EtOAc, and concentrated. Purification by column chromatography using 1:1 hexanes-EtOAc as eluent afforded 114 mg (52%) of the title as a white solid, mp 224-225 °C. Mass Spec: 576 $(M+H)^+$.

Example 138

1-(2, 6-dichloro-4-formylphenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo [3,4-d]pyrimidin-4-one

A two-neck flask was flame-dried, charged with 1-(4-bromo-2, 6-dichlorophenyl)-3-isopropyl-6-(3-methoxy benzyl)pyrazolo[3,4-d]pyrimidin-4-one (250 mg, 0.48 mmol) and 4 mL of THF, and placed under an argon atmosphere. The solution was cooled to 0 °C and isopropylmagnesium chloride (0.26 mL, 0.523 mmol) was added dropwise via syringe. The reaction was stirred at -78 °C for 2 min and DMF (0.08 mL, 1.06 mmol) was added via syringe. The reaction was stirred at -78 °C for 15 min and at RT for 30 min. The reaction was quenched with 10% aq. citric acid and extracted with EtOAc. The organic extract was washed with water then brine, dried (MgSO4), and evaporated. Purification by column chromatography on silica gel using 2:1 hexanes-EtOAc as eluent afforded 68 mg (30%) of the title as a white solid, mp 212-214 °C. Mass Spec: 469$(M-H)^-$.

Starting from the appropriate 3-substituted 5-amino-1-arylpyrazole-4-carboxamides the following compounds were prepared by methods similiar to those used to synthesize compounds in the examples and tables above:

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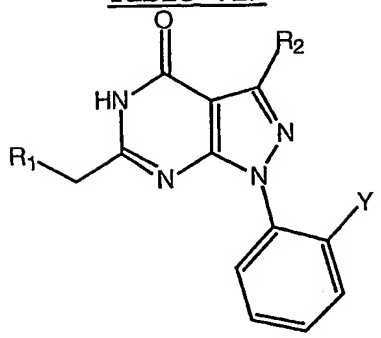
Table VII



Ex.#	Y	R^2	R^1	mp. (°C)	MS
139	Cl	Et	4-Methoxyphenyl	Amorphous	393
140	Cl	Et	4-Hydroxyphenyl	Amorphous	379
141	Cl	Et	3-Methoxyphenyl	Amorphous	393
142	Cl	Et	3-Hydroxyphenyl	Amorphous	379
143	Cl	*i*-Pr	3-Hydroxyphenyl	227-228	395
144	Cl	*i*-Pr	4-Aminophenyl	Amorphous	394
145	Cl	*i*-Pr	3-Methoxyphenyl		407
146	Cl	*i*-Pr	4-Methoxyphenyl	Amorphous	407
147	Cl	*i*-Pr	4-Hydroxyphenyl	Amorphous	395
148	Cl	Et	4-(*N*,*N*-dimethyl-glycinamido)phenylHCl		479
149	Cl	SCH_3	4-Hydroxyphenyl	243-244	397
150	Cl	SCH_3	4-Methoxyphenyl	227-228	413
151	Br	Et	3-Methoxyphenyl	178-180	439
152	Br	Et	4-Aminophenyl	246-249	424
153	Br	Et	3-Hydroxyphenyl	199-201	425
154	F	Et	3-Methoxyphenyl	193-194	379
155	F	Et	3-Hydroxyphenyl	235-237	365
156	Br	Et	4-(*N*,*N*-dimethyl-glycinamido)phenyl	156-158	509
157	F	Et	4-Aminophenyl	231-233	364

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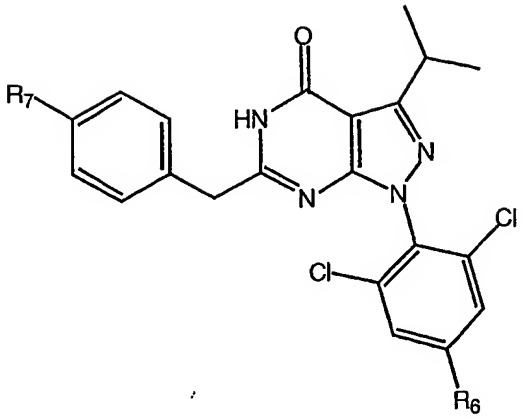
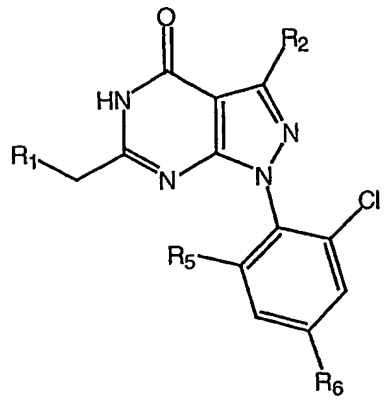
Table VIII



Ex. #	R^6	R^7	mp. (°C)	MS
158	H	$CH_3NHCH_2CH_2N(CH_3)COCH_2$	154-155	541
159	H	$H_2NCH_2CH_2NHCOCH_2$	140-142	513
160	H	Piperazin-1-ylCOCH$_2$	181-183	539
161	H	$CH_3CH_2NHCOCH_2$	242-244	496
162	H	$CH_3NHCOCH_2$	249-250	482
163	H	1-CH_3-piperazin-4-ylCOCH$_2$	236-237	553
164	H	$(CH_3)_2NCH_2CH_2N(CH_3)COCH_2$	134-136	555
165	Cl	4-CH_3-piperazin-1-ylCOCH$_2$	205-207	587

Table IX

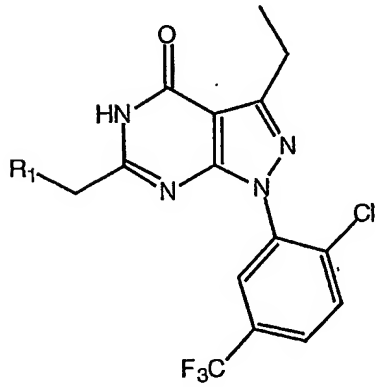


Ex.#	R^5	R^6	R^2	R^1	mp. (°C)	MS
166	Cl	CF_3	Et	3-Methoxyphenyl	192-193	497
167	Cl	CF_3	Et	4-Aminophenyl	235-236	495
168	Cl	CF_3	Et	4-Methoxyphenyl	240-241	497
169	Cl	Br	Et	4-Hydroxyphenyl	284-286	493
170	Cl	Br	Et	3-Hydroxyphenyl	242-244	495
171	Cl	H	Et	4-Hydroxyphenyl	262-263	413
172	Cl	H	Et	4-Aminoxyphenyl	159-161	414
173	Cl	H	Et	3-Hydroxyphenyl	242-244	413
174	Cl	Br	Et	3-Methoxyphenyl	232-233	507
175	Cl	Br	Et	4-Methoxyphenyl	252-253	507
176	Cl	H	Et	4-Methoxyphenyl	220-222	427
177	Cl	H	Et	3-Methoxyphenyl	186-187	427
178	F	H	SCH_3	4-Hydroxyphenyl	267-268	415
179	F	H	SCH_3	3-Hydroxyphenyl	252-253	415
180	Cl	Br	SCH_3	4-Hydroxyphenyl	255-256	511
181	F	H	SCH_3	4-Methoxyphenyl	193-194	429
182	F	H	SCH_3	3-Methoxyphenyl	244-245	431
183	Cl	Br	SCH_3	4-Methoxyphenyl	267-268	524
184	Me	H	Et	4-Hydroxyphenyl	255-256	395
185	Me	Cl	SCH_3	4-Methoxyphenyl	252-255	459
186	Me	H	SCH_3	4-Methoxyphenyl	233-235	425
187	Me	Cl	Et	4-Methoxyphenyl	245-246	441
188	Me	Cl	SCH_3	4-Hydroxyphenyl	277-279	445
189	Me	Cl	Et	4-Hydroxyphenyl	Amorphous	429

190	Me	H	SCH_3	4-Hydroxyphenyl	264-266	413
191	Me	H	Et	4-Methoxyphenyl	220-221	409
192	Me	H	Et	4-Hydroxyphenyl	257-259	395
193	Me	H	Et	3-Methoxyphenyl	188-190	409
194	Me	H	Et	4-Hydroxyphenyl	255-256	395
195	Cl	CO_2H	Et	4-Methoxyphenyl	292-294	
196	Cl	CO_2H	Et	4-Hydroxyphenyl	308-310	457
197	Cl	CO_2H	Et	3-Methoxyphenyl	Amorphous	471
198	Cl	CO_2H	Et	3-Hydroxyphenyl	280-282	
199	Me	H	*i*-Pr	4-Aminophenyl	205-206	408
200	Me	H	*i*-Pr	4-(*N*,*N*-Dimethylglycin amido)phenyl	277-279	491
201	Cl	CONHMe	Et	4-Methoxyphenyl	278-280	486
202	Me	H	Et	4-Methoxyphenyl	220-221	409
203	Me	H	Et	4-Hydroxyphenyl	257-259	395
204	Me	H	Et	3-Methoxyphenyl	188-190	409
205	Cl	CO_2H	Et	4-Aminophenyl	226-228	458
206	Cl	Cl	*t*-Bu	3-Hydroxy-4-methoxy phenyl		505
207	Cl	Cl	CHF_2	3-Hydroxy-4-methoxy phenyl		499
208	Cl	Cl	CH_2OH	3-Methoxyphenyl	227-229	
209	Cl	Cl	*i*-Pr	3-(Ethoxycarbonyl-methyl)phenyl	174-175	
210	Cl	Cl	*i*-Pr	3-(carboxymethyl) phenyl	210-211	
211	Cl	Cl	*i*-Pr	3-(2-hydroxyethyl) phenyl		489
212	Cl	Cl	*n*-Bu	3-Hydroxy-4-methoxy phenyl		505
213	Me	H	*i*-Pr	4-(1-CH_3-piperidin-4-ylN(CH_3)CH_2CONH)phenyl		576
214	Me	H	*i*-Pr	4-(1-CH_3-piperidin-4-ylN(CH_3)CONH)phenyl		562
215	Me	Cl	*i*-Pr	4-(1-CH_3-piperidin-4-ylN(CH_3)CONH)phenyl		596
216	Me	Cl	*i*-Pr	4-(1-CH_3-piperidin-4-	108-110	610

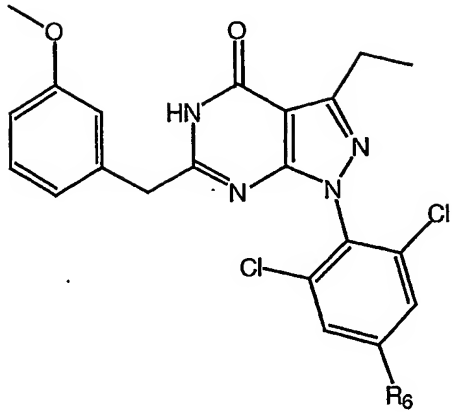
				ylN(CH_3)CH_2CONH)phenyl		
217	Me	Cl	*i*-Pr	4-aminophenyl	212-213	442
218	Me	Cl	*i*-Pr	4-(morpholin-4-ylCONH)phenyl	256-258	555
219	Me	Cl	*i*-Pr	4-(4-CH_3-piperazin-1-ylCONH)phenyl	154-156	568
220	Me	Cl	*i*-Pr	4-(4-CH_3-piperazin-1-ylCH_2CONH)phenyl	199-210	582
221	Me	Cl	*i*-Pr	4-(Me_2NCH_2CONH)phenyl HCl	>300	561
222	Me	Cl	*i*-Pr	4-(morpholin-4-yl CH_2CONH)phenyl	246-249	569
223	Cl	Cl	*i*-Pr	5-(Me_2NCH_2)-1-methyl pyrrol-2-yl	182-184	507
224	Cl	CH_2NH_2	*i*-Pr	3-Methoxyphenyl		472
225	Cl	SO_2NH_2	*i*-Pr	3-Methoxyphenyl	244-245	520

Table X



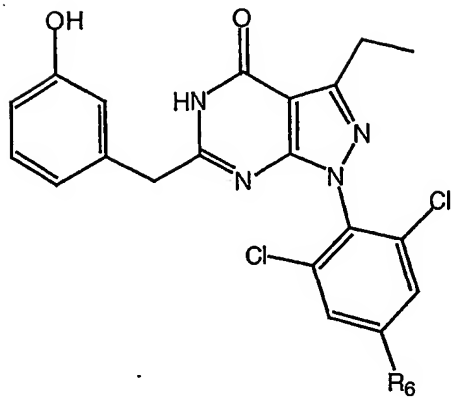
Ex. #	R^1	mp. (°C)	MS
226	4-(*N*,*N*-Dimethyl glycinamido)phenyl	235-237	533
227	3-Hydroxyphenyl	227-229	449

Table XI



Ex.#	R^6	mp(°C)	MS
228	$CONHCH_2CH_2N(CH_3)_2$	203-205	543
229	$CONHCH_2CH_2CH_3$	229-231	512
230	$CONHCH(CH_3)_2$	233-235	512
231	$CONHCH_2Ph$	239-240	560
232	CO-(4-CH_3-piperazin)-1-yl	128-130	555
233	$CONHCH_2$pyridin-3-yl	Amorphous	563
234	$CONHCH_2$pyridin-2-yl	188-190	563
235	$CONHCH_2$pyridin-4-yl	238-239	563
236	$CONHCH_2CH_3$	226-228	498
237	CONHPh	Amorphous	546
238	$CONHC(CH_3)_3$	222-224	528
239	CO-piperazin-1-yl	Amorphous	541
240	CONHcyclo-C_3H_5	236-239	510
241	CONHpyridin-3-yl	256-258	549
242	CONHpyridin-4-yl	Amorphous	549
243	CONH(4-CH_3-piperazin)-1-yl	Amorphous	570
244	CONHpyridin-2-yl	237-239	549
245	$CONHOCH_3$	204-206	502

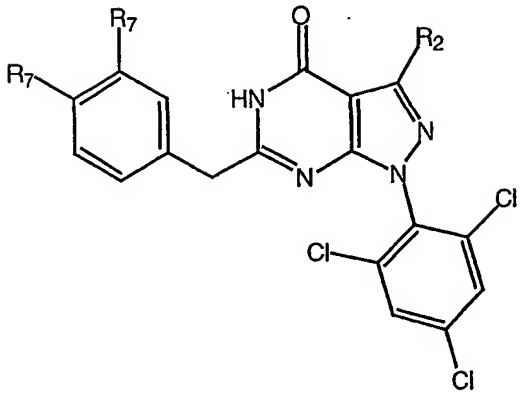
Table XII



Ex.#	R^5	mp(°C)	MS
246	$CONHCH_2CH_2N(CH_3)_2$	263-265	529
247	$CONHCH_2Ph$	247-249	546

By reacting a *p*-substituted aniline with suitable acylating agents and performing further synthetic manipulations as necessary, the following compounds were prepared:

Table XIII



Ex.#	R^2	R^7 (para)	R^7(meta)	mp(°C)	MS
248	*c*-Pr	$(CH_3)_2NCH_2CONH$	H		545
249	Et	CH_3CONH	H		488
250	Et	CH_3OCONH	H		504
251	Et	$CH_3NHCONH$	H		503
252	*i*-Pr	CH_3OCONH	H		518
253	*i*-Pr	CH_3OCON(Me)	H		532
254	Et	$(CH_3)_2NCH_2CONH$	H		531
255	*i*-Pr	$CH_3NHCONH$	HO		535
256	*i*-Pr	CH_3NHCON(Me)	H	235-237	531
257	*i*-Pr	4-CH_3-piperazin-1-ylN(Me)	H		616
258	*i*-Pr	$(CH_3)_2NCH_2CON$(Me)	H	235-237	561
259	*i*-Pr	CH_3NHCON(Me)	H	235-237	531
260	*i*-Pr	$(CH_3)_2NCH_2CONH$	HO	255-258	563
261	*i*-Pr	(+/-)-$(CH_3)_2NCH(CH_3)CONH$	H		561
262	*i*-Pr	$(CH_3)_2NCH_2CONH$	MeO	Amorphous	577
263	*i*-Pr	$CH_3NHCONH$	MeO	258-261	
264	*i*-Pr	imidazol-1-ylCH_2CONH	HO		586
265	*i*-Pr	$(CH_3)_2NCH_2CONH$	H	255-257	547
266	*i*-Pr	4-CH_3-piperazin-1-yl CH_2CONH	H		602
267	*i*-Pr	$CH_3NHCONH$	H	268-274	519
268	*i*-Pr	Morpholin-4-ylCH_2CONH	H	252-255	589
269	*i*-Pr	Azetidin-1-ylCH_2CONH	H		559
270	*i*-Pr	$(CH_3)_2NCH_2CH_2SO_2NH$	H		597.1011

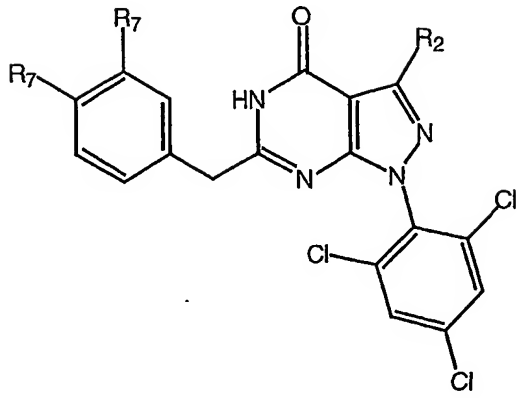
271	*i*-Pr	$EtO_2CCH_2NHCONH$	H	229-230	589
272	*i*-Pr	Hydantoin-1-yl	H	>300	543
273	*i*-Pr	$HOCH_2CH_2NHCONH$	H	160-162	547.0799
274	*i*-Pr	$HO_2C(CH_2)_2CONH$	H	256-258	560
275	*i*-Pr	Imidazol-1-ylCH_2CONH	H	276-278	570
276	*i*-Pr	Morpholin-4-ylCH_2CH_2 NHCSNH	H		634
277	*i*-Pr	$HO_2CCH_2NHCONH$	H		561
278	*i*-Pr	$HO_2C(CH_2)_3CONH$	H		574
279	*i*-Pr	H_2NCH_2CONH	H	>300	519
280	*i*-Pr	CH_3NHCH_2CONH	H	Amorphous	533.1029
281	*i*-Pr	4-F-phenyl CH_2NHCH_2CONH	H	217-223	627
282	*i*-Pr	Pyrrolidin-1-ylCH_2CONH	H	235-240	573
283	*i*-Pr	pyrid-2-ylCH_2NHCH_2CONH	H		610
284	*i*-Pr	pyrid-3-ylCH_2NHCH_2CONH	H	145-150	610
285	*i*-Pr	pyrid-4-ylCH_2NHCH_2CONH	H	180-185	610
286	*i*-Pr	$BocNHCH_2CH_2NHCH_2CONH$	H		662.1829
287	*i*-Pr	$HOCH_2CH(CH_3)NHCH_2CONH$	H	190-192	577
288	*i*-Pr	$CH_3CH(OH)CH_2NHCH_2CONH$		152-160	577
289	*i*-Pr	$H_2NCH_2CH_2NHCH_2CONH$	H		562
290	*i*-Pr	Morpholin-4-ylCH_2CH_2 $NHCH_2CONH$	H		632
291	*i*-Pr	1-CH_3-piperidin-4-yl $N(CH_3)CH_2CONH$	H		630
292	*i*-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$	H	188-190	604
293	*i*-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CONH$	H		590
294	*i*-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$	OH		606
295	*i*-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$	OMe		620
296	*i*-Pr	$(CH_3)_2NCH(CH_3)CONH$	H		561
297	*i*-Pr	1-CH_3-L-prolylNH	H		
298	*i*-Pr	Homopiperazin-1-yl CH_2CONH	H		602.1610
299	*i*-Pr	$CH_3CH_2NHCH_2CONH$	H		547
300	*i*-Pr	4-(H_2NCH_2)piperidin-1-yl CH_2CONH	H	Amorphous	616
301	*i*-Pr	$(CH_3)_2NCH_2CH_2NHCH_2CONH$	H	133-135	590.1610
302	*i*-Pr	*Cyclo*-$C_3H_5NHCH_2CONH$	H	213-216	559

303	*i*-Pr	Piperidin-4-ylCH_2NH CH_2CONH	H		616
304	*i*-Pr	$HO(CH_2)_3NHCH_2CONH$	H	200-205	575
305	*i*-Pr	1-Bocpiperidin-4-ylCH_2NH CH_2CONH	H		716
306	*i*-Pr	$HOCH_2CH_2NHCH_2CONH$	H	210-212	563
307	*i*-Pr	*Cyclo*-$C_4H_7NHCH_2CONH$	H	225-228	573
308	*i*-Pr	Azetidin-3-ylCONH	H		545
309	*i*-Pr	D-prolylNH·HCl	H	225-226	559
310	*i*-Pr	Boc-D-prolylNH	H		559.1185
311	*i*-Pr	L-prolylNH·HCl	H	225-226	659.1707
312	*i*-Pr	Boc-L-prolylNH	H		657
313	*i*-Pr	Piperidin-1-yl$CH_2CH_2NHCH_2CONH$	H	213-215	630
314	*i*-Pr	$(CH_3)_2CHNHCH_2CONH$	H	130-135	559
315	*i*-Pr	$BocNHCH_2CH_2CONH$	H		631
316	*i*-Pr	piperazin-2-yl-CONH	H	Amorphous	547.1286
317	*i*-Pr	4-Me-piperazin-2-yl-CONH	H	Amorphous	588.1448
318	*i*-Pr	piperidin-1-ylNHCONH	H	264-266	588
319	*i*-Pr	$H_2NCH_2CH_2NHCONH·F_3CCO_2H$	H		548
320	*i*-Pr	pyrid-2-ylNHCONH	H	277-281	
321	*i*-Pr	$(CH_3)_2NCH_2CH_2NHCONH$	H	220-222	576
322	*i*-Pr	$(CH_3)_2NCH_2CH_2NHCONH$	OMe	244-248	606
323	*i*-Pr	$BocNHCH_2CH_2NHCONH$	H	208-210	646
324	*i*-Pr	$HO(CH_2)_4NHCONH$	H	208-210	577
325	*i*-Pr	$(CH_3)_2NNHCONH$	H	240-242	546
326	*i*-Pr	$(CH_3)_2N(CH_2)_3NHCONH$	H		590
327	*i*-Pr	$(CH_3)_2N(CH_2)_3NHCONH$	OMe	226-228	620
328	*i*-Pr	4-CH_3-homo-piperazin-1-yl-CONH	H		602
329	*i*-Pr	$CH_3SO_2NHCONH$	H		581
330	*i*-Pr	$CH_3ONHCONH$	H		534
331	*i*-Pr	1-CH_3-piperidin-4-yl $N(CH_3)CONH$	H		616
332	*i*-Pr	1-CH_3-piperidin-4-yl $N(CH_3)CONH$	OH		632
333	*i*-Pr	1-CH_3-piperidin-4-yl	OMe	243-245	646

		$N(CH_3)CONH$			
334	*i*-Pr	Tetrahydrofur-2-yl $CH_2NHCONH$	H		587
335	*i*-Pr	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$	H		589
336	*i*-Pr	$HOCH_2CH(CH_3)NHCONH$	H	156-158	561
337	*i*-Pr	$CH_3CH(OH)CH_2NHCONH$	H		561
338	*i*-Pr	$HOCH_2CH_2NHCONH$	H	222-225	547
339	*i*-Pr	Morpholin-4-ylNHCONH	H	272-274	588
340	*i*-Pr	$(CH_3)_2NCH(CH_3)CH_2NHCONH$	H		590
341	*i*-Pr	4-CH_3-piperazin-1-yl NHCONH	H		603
342	*i*-Pr	4-CH_3-piperazin-1-yl NHCONH	OH		619
343	*i*-Pr	4-CH_3-piperazin-1-yl NHCONH	OMe	245-246	633
344	*i*-Pr	Morpholin-4-yl $CH_2CH_2NHCONH$	H		618
345	*i*-Pr	4-CH_3-piperazin-1-ylCONH	H		588
346	*i*-Pr	Piperazin-1-ylCONH ·HCl	H		574
347	Et	4-CH_3-piperazin-1-ylCONH	H		574
348	Et	$(CH_3)_2NCH_2CH_2NHCONH$	H		563
349	Et	pyrid-2-ylNHCONH	H	Amorphous	582
350	Et	pyrid-4-ylNHCONH	H	Amorphous	582
351	*i*-Pr	H	MeNHCONHCH$_2$		533
352	*i*-Pr	(+/-)-2-(Me_2NCH_2)piperid-1-ylCONH	H		630
353	*i*-Pr	(+/-)-2-(Me_2NCH_2)piperid-1-ylCONH ·CF_3CO_2H	OH		646
354	*i*-Pr	(+/-)-2-(Me_2NCH_2)piperid-1-ylCONH	OMe	131-135	660
355	*i*-Pr	$CH_3NCH_2CH_2N(CH_3)CONH$	OMe	146-148	606
356	*i*-Pr	$(CH_3)_2NCH_2CH_2NCO$	H	278-280	561
357	*i*-Pr	$(CH_3)NCH_2CH_2N(CH_3)CO$	H		561
358	*i*-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CO$	H		575

Following procedures similar to those used to synthesize the examples above, the following compounds were prepared or could be prepared:

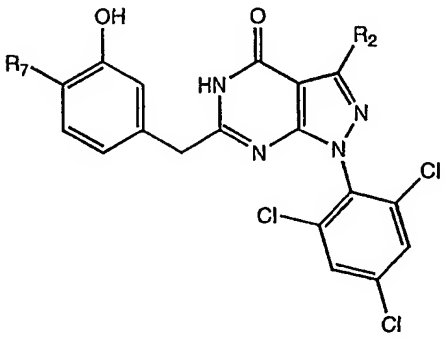
Table XIV



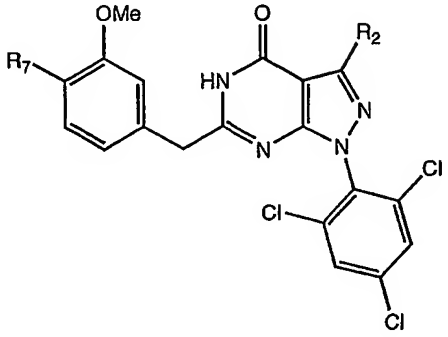
Ex.#	R^2	R^7(para)	R^7(meta)	MS
1	*i*-Pr	Pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$	H	616
2	*i*-Pr	Pyrrolidin-1-yl$CH_2CH_2NHCONH$	OMe	632
3	*i*-Pr	pyrrolidin-1-yl$CH_2CH_2NHCONH$	OH	618
4	*i*-Pr	pyrrolidin-1-yl$CH_2CH_2NHCONH$	H	602
5	*i*-Pr	2-CH_3-piperazin-1-ylCONH	H	
6	*i*-Pr	3-CH_3-piperazin-1-ylCH_2CONH	H	602
7	*i*-Pr	*trans*-2,5-di-CH_3-piperazin-1-ylCH_2CONH	H	616
8	*i*-Pr	*cis*-2,6-di-CH_3-piperazin-1-ylCH_2CONH	H	
9	*i*-Pr	*cis*-3,4-di-CH_3-piperazin-1-ylCH_2CONH	H	616
10	*i*-Pr	*cis*-3,5-di-CH_3-piperazin-1-ylCH_2CONH	H	
11	*i*-Pr	*trans*-2,6-di-CH_3-piperazin-1-ylCH_2CONH	H	
12	*i*-Pr	*trans*-3,5-di-CH_3-piperazin-1-ylCH_2CONH	H	
13	*i*-Pr	(*R*)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$	H	
14	*i*-Pr	(*S*)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$	H	
15	*i*-Pr	5-CH_3-pyrazin-2-ylCH_2NHCH_2CONH	H	
16	*i*-Pr	$(CH_3)_2NCH_2CH_2CH_2OCONH$	H	591
17	*i*-Pr	(+/-)-*N*-(CH_3)piperidin-3-ylCH_2OCONH	H	617
18	*i*-Pr	(+/-)-*N*-(CH_3)piperidin-3-ylOCONH	H	603
19	*i*-Pr	(+/-)-*N*-(CH_3)piperidin-2-ylCH_2OCONH	H	617
20	*i*-Pr	(+/-)-*N*-(CH_3)pyrrolidin-3-ylOCONH	H	589
21	*i*-Pr	2-CH_3-piperazin-1-ylCH_2CONH	H	
22	*i*-Pr	pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$	H	
23	*i*-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CONH$	H	590
24	*i*-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CO$	H	575
25	*i*-Pr	2-CH_3-piperazin-1-ylCONH	H	
26	*i*-Pr	3-CH_3-piperazin-1-ylCH_2CONH	H	

27	*i*-Pr	*trans*-2,5-di-CH_3-piperazin-1-ylCH_2CONH	H
28	*i*-Pr	*cis*-2,6-di-CH_3-piperazin-1-ylCH_2CONH	H
29	*i*-Pr	*cis*-3,5-di-CH_3-piperazin-1-ylCH_2CONH	H
30	*i*-Pr	*trans*-2,6-di-CH_3-piperazin-1-ylCH_2CONH	H

Table XV



(a)



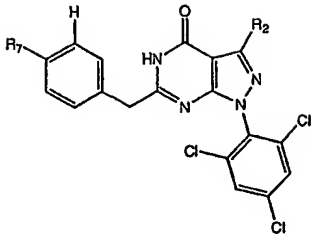
(b)

Ex.#	R^2	R^7
1	i-Pr	1-CH_3-piperazin-4-ylCH_2CONH
2	i-Pr	$BocNHSO_2NH$
3	i-Pr	Morpholin-4-ylCH_2CONH
4	i-Pr	Azetidin-1-ylCH_2CONH
5	i-Pr	$(CH_3)_2NCH_2CH_2SO_2NH$
6	i-Pr	$EtO_2CCH_2NHCONH$
7	i-Pr	$HOCH_2CH_2NHCONH$
8	i-Pr	Hydantoin-1-yl
9	i-Pr	$HOCH_2CH_2NHCONH$
10	i-Pr	$HO_2C(CH_2)_2CONH$
11	i-Pr	imidazol-1-ylCH_2CONH
12	i-Pr	Morpholin-4-yl$CH_2CH_2NHCSNH$
13	i-Pr	$HO_2CCH_2NHCONH$
14	i-Pr	$HO_2C(CH_2)_3CONH$
15	i-Pr	$(CH_3)_2NCH_2CONH$
16	i-Pr	H_2NCH_2CONH
17	i-Pr	CH_3NHCH_2CONH
18	i-Pr	4-F-phenylCH_2NHCH_2CONH
19	i-Pr	pyrrolidin-1-ylCH_2CONH
20	i-Pr	pyrid-2-ylCH_2NHCH_2CONH
21	i-Pr	pyrid-3-ylCH_2NHCH_2CONH

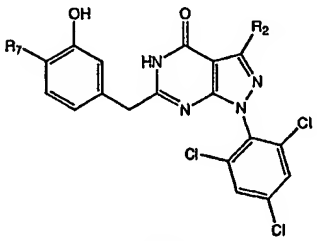
22	i-Pr	pyrid-4-ylCH$_2$NHCH$_2$CONH
23	i-Pr	BocNHCH$_2$CH$_2$NHCH$_2$CONH
24	i-Pr	HOCH$_2$CH(CH$_3$)NHCH$_2$CONH
25	i-Pr	CH$_3$CH(OH)CH$_2$NHCH$_2$CONH
26	i-Pr	H$_2$NCH$_2$CH$_2$NHCH$_2$CONH
27	i-Pr	morpholin-4-ylCH$_2$CH$_2$NHCH$_2$CONH
28	i-Pr	1-CH$_3$-piperidin-4-ylN(CH$_3$)CH$_2$CONH
29	i-Pr	(CH$_3$)$_2$NCH$_2$CH$_2$N(CH$_3$)CH$_2$CONH
30	i-Pr	piperazin-1-ylCH$_2$CONH
31	i-Pr	(CH$_3$)$_2$NCH(CH$_3$)CONH
32	i-Pr	1-CH$_3$-L-prolylNH
33	i-Pr	Homopiperazin-1-ylCH$_2$CONH
34	i-Pr	CH$_3$CH$_2$NHCH$_2$CONH
35	i-Pr	4-(CH$_2$NH$_2$)piperidin-1-ylCH$_2$CONH
36	i-Pr	(CH$_3$)$_2$NCH$_2$CH$_2$NHCH$_2$CONH
37	i-Pr	H$_2$NCH$_2$CONH
38	i-Pr	*cyclo*-C$_3$H$_5$NHCH$_2$CONH
39	i-Pr	piperidin-4-ylCH$_2$NHCH$_2$CONH
40	i-Pr	HO(CH$_2$)$_3$NHCH$_2$CONH
41	i-Pr	1-Bocpiperidin-4-ylCH$_2$NHCH$_2$CONH
42	i-Pr	HOCH$_2$CH$_2$NHCH$_2$CONH
43	i-Pr	*cyclo*-C$_4$H$_7$NHCH$_2$CONH
44	i-Pr	azetidin-3-ylCONH
45	i-Pr	D-prolylNH·HCl
46	i-Pr	Boc-D-prolylNH
47	i-Pr	L-prolylNH·HCl
48	i-Pr	Boc-L-prolylNH
49	i-Pr	piperidin-1-ylCH$_2$CH$_2$NHCH$_2$CONH
50	i-Pr	(CH$_3$)$_2$CHNHCH$_2$CONH
51	i-Pr	BocNHCH$_2$CH$_2$CONH
52	i-Pr	pyrrolidin-1-ylCH$_2$CH$_2$NHCH$_2$CONH
53	i-Pr	2-CH$_3$-piperazin-1-ylCONH
54	i-Pr	3-CH$_3$-piperazin-1-ylCH$_2$CONH
55	i-Pr	trans-2,5-di-CH$_3$-piperazin-1-ylCH$_2$CONH
56	i-Pr	cis-2,6-di-CH$_3$-piperazin-1-ylCH$_2$CONH
57	i-Pr	cis-3,5-di-CH$_3$-piperazin-1-ylCH$_2$CONH
58	i-Pr	trans-2,6-di-CH$_3$-piperazin-1-ylCH$_2$CONH

59	i-Pr	trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH
60	i-Pr	(R)-1-Ethylpyrrolidin-2-ylCH_2NHCONH
61	i-Pr	(S)-1-Ethylpyrrolidin-2-ylCH_2NHCONH
62	i-Pr	5-CH_3-pyrazin-2-ylCH_2NHCH_2CONH
63	i-Pr	piperazin-2-yl-CONH
64	i-Pr	4-Me-piperazin-2-ylCONH

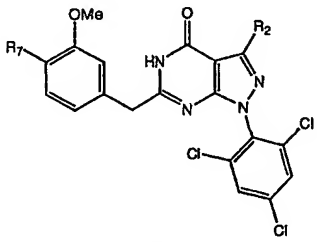
Table XVI



(a)



(b)



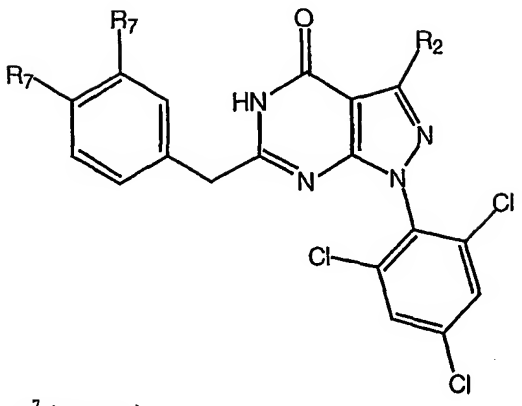
(c)

Ex.#	R^2	R^7
1	*Cyc-Bu*	$(CH_3)_2NCH_2CONH$
2	*Cyc-Bu*	1-CH_3-piperazin-4-ylCH_2CONH
3	*Cyc-Bu*	$CH_3NHCONH$
4	*Cyc-Bu*	Morpholin-4-ylCH_2CONH
5	*Cyc-Bu*	Azetidin-1-ylCH_2CONH
6	*Cyc-Bu*	$(CH_3)_2NCH_2CH_2SO_2NH$
7	*Cyc-Bu*	$EtO_2CCH_2NHCONH$
8	*Cyc-Bu*	Hydantoin-1-yl
9	*Cyc-Bu*	$HOCH_2CH_2NHCONH$
10	*Cyc-Bu*	$HO_2C(CH_2)_2CONH$
11	*Cyc-Bu*	imidazol-1-ylCH_2CONH
12	*Cyc-Bu*	Morpholin-4-yl$CH_2CH_2NHCSNH$
13	*Cyc-Bu*	$HO_2CCH_2NHCONH$
14	*Cyc-Bu*	$HO_2C(CH_2)_3CONH$
15	*Cyc-Bu*	H_2NCH_2CONH
16	*Cyc-Bu*	CH_3NHCH_2CONH
17	*Cyc-Bu*	4-F-phenylCH_2NHCH_2CONH
18	*Cyc-Bu*	pyrrolidin-1-ylCH_2CONH
19	*Cyc-Bu*	pyrid-2-ylCH_2NHCH_2CONH
20	*Cyc-Bu*	pyrid-3-ylCH_2NHCH_2CONH

21	*Cyc-Bu*	pyrid-4-ylCH$_2$NHCH$_2$CONH
22	*Cyc-Bu*	BocNHCH$_2$CH$_2$NHCH$_2$CONH
23	*Cyc-Bu*	HOCH$_2$CH(CH$_3$)NHCH$_2$CONH
24	*Cyc-Bu*	CH$_3$CH(OH)CH$_2$NHCH$_2$CONH
25	*Cyc-Bu*	H$_2$NCH$_2$CH$_2$NHCH$_2$CONH
26	*Cyc-Bu*	morpholin-4-ylCH$_2$CH$_2$NHCH$_2$CONH
27	*Cyc-Bu*	1-CH$_3$-piperidin-4-ylN(CH$_3$)CH$_2$CONH
28	*Cyc-Bu*	(CH$_3$)$_2$NCH$_2$CH$_2$N(CH$_3$)CH$_2$CONH
29	*Cyc-Bu*	(CH$_3$)$_2$NCH(CH$_3$)CONH
30	*Cyc-Bu*	1-CH$_3$-L-prolylNH
31	*Cyc-Bu*	Homopiperazin-1-ylCH$_2$CONH
32	*Cyc-Bu*	CH$_3$CH$_2$NHCH$_2$CONH
33	*Cyc-Bu*	4-(CH$_2$NH$_2$)piperidin-1-ylCH$_2$CONH
34	*Cyc-Bu*	(CH$_3$)$_2$NCH$_2$CH$_2$NHCH$_2$CONH
35	*Cyc-Bu*	*cyclo*-C$_3$H$_5$NHCH$_2$CONH
36	*Cyc-Bu*	Piperidin-4-ylCH$_2$NHCH$_2$CONH
37	Cyc-Bu	HO(CH$_2$)$_3$NHCH$_2$CONH
38	*Cyc-Bu*	1-Bocpiperidin-4-ylCH$_2$NHCH$_2$CONH
39	Cyc-Bu	HOCH$_2$CH$_2$NHCH$_2$CONH
40	*Cyc-Bu*	*cyclo*-C$_4$H$_7$NHCH$_2$CONH
41	*Cyc-Bu*	azetidin-3-ylCONH
42	*Cyc-Bu*	D-prolylNH·HCl
43	*Cyc-Bu*	Boc-D-prolylNH
44	*Cyc-Bu*	L-prolylNH·HCl
45	*Cyc-Bu*	Boc-L-prolylNH
46	*Cyc-Bu*	piperidin-1-ylCH$_2$CH$_2$NHCH$_2$CONH
47	*Cyc-Bu*	(CH$_3$)$_2$CHNHCH$_2$CONH
48	*Cyc-Bu*	BocNHCH$_2$CH$_2$CONH
49	*Cyc-Bu*	piperazin-2-yl-CONH
50	*Cyc-Bu*	4-Me-piperazin-2-yl-CONH
51	*Cyc-Bu*	piperidin-1-ylNHCONH
52	*Cyc-Bu*	H$_2$NCH$_2$CH$_2$NHCONH·F$_3$CCO$_2$H
53	*Cyc-Bu*	pyrid-2-ylNHCONH
54	*Cyc-Bu*	(CH$_3$)$_2$NCH$_2$CH$_2$NHCONH
55	*Cyc-Bu*	BocNHCH$_2$CH$_2$NHCONH
56	*Cyc-Bu*	HO(CH$_2$)$_4$NHCONH
57	*Cyc-Bu*	(CH$_3$)$_2$NNHCONH

58	*Cyc-Bu*	$(CH_3)_2N(CH_2)_3NHCONH$
59	*Cyc-Bu*	1-CH_3-homopiperazin-4-yl-CONH
60	*Cyc-Bu*	$CH_3SO_2NHCONH$
61	*Cyc-Bu*	$CH_3ONHCONH$
62	*Cyc-Bu*	$(CH_3)_2NCH_2CH_2NHCONH$
63	*Cyc-Bu*	1-CH_3-piperidin-4-yl$N(CH_3)CONH$
64	*Cyc-Bu*	tetrahydrofur-2-yl$CH_2NHCONH$
65	*Cyc-Bu*	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$
66	*Cyc-Bu*	$HOCH_2CH(CH_3)NHCONH$
67	*Cyc-Bu*	$CH_3CH(OH)CH_2NHCONH$
68	*Cyc-Bu*	$HOCH_2CH_2NHCONH$
69	*Cyc-Bu*	morpholin-4-ylNHCONH
70	*Cyc-Bu*	$(CH_3)_2NCH(CH_3)CH_2NHCONH$
71	*Cyc-Bu*	1-CH_3-piperazin-4-ylNHCONH
72	*Cyc-Bu*	morpholin-4-yl$CH_2CH_2NHCONH$
73	*Cyc-Bu*	1-CH_3-piperazin-4-ylCONH
74	*Cyc-Bu*	pyrid-2-ylNHCONH
75	*Cyc-Bu*	pyrid-4-ylNHCONH
76	Cyc-Bu	pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$
77	Cyc-Bu	2-CH_3-piperazin-1-ylCONH
78	Cyc-Bu	3-CH_3-piperazin-1-ylCH_2CONH
79	Cyc-Bu	trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH
80	Cyc-Bu	cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH
81	Cyc-Bu	cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH
82	Cyc-Bu	trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH
83	Cyc-Bu	trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH
84	Cyc-Bu	(R)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
85	Cyc-Bu	(S)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
86	Cyc-Bu	5-CH_3-pyrazin-2-ylCH_2NHCH_2CONH

Table XVII

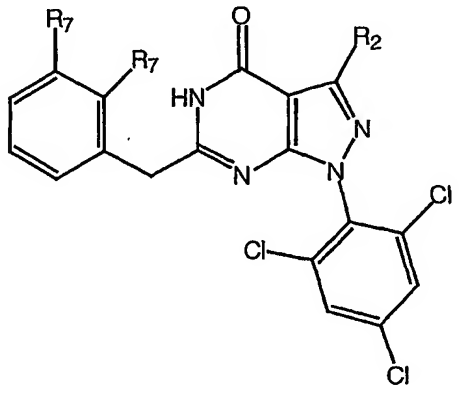


Ex.#	R^2	R^7(para)	R^7(meta)
1	*i-Pr*	$(CH_3)_2NCH_2CONH$	Me
2	*i-Pr*	1-CH_3-piperazin-4-ylCH_2CONH	Me
3	*i-Pr*	$CH_3NHCONH$	Me
4	*i-Pr*	Morpholin-4-ylCH_2CONH	Me
5	*i-Pr*	Azetidin-1-ylCH_2CONH	Me
6	*i-Pr*	$(CH_3)_2NCH_2CH_2SO_2NH$	Me
7	*i-Pr*	$EtO_2CCH_2NHCONH$	Me
8	*i-Pr*	Hydantoin-1-yl	Me
9	*i-Pr*	$HOCH_2CH_2NHCONH$	Me
10	*i-Pr*	$HO_2C(CH_2)_2CONH$	Me
11	*i-Pr*	imidazol-1-ylCH_2CONH	Me
12	*i-Pr*	Morpholin-4-yl$CH_2CH_2NHCSNH$	Me
13	*i-Pr*	$HO_2CCH_2NHCONH$	Me
14	*i-Pr*	$HO_2C(CH_2)_3CONH$	Me
15	*i-Pr*	H_2NCH_2CONH	Me
16	*i-Pr*	CH_3NHCH_2CONH	Me
17	*i-Pr*	4-F-phenylCH_2NHCH_2CONH	Me
18	*i-Pr*	pyrrolidin-1-ylCH_2CONH	Me
19	*i-Pr*	pyrid-2-ylCH_2NHCH_2CONH	Me
20	*i-Pr*	pyrid-3-ylCH_2NHCH_2CONH	Me
21	*i-Pr*	pyrid-4-ylCH_2NHCH_2CONH	Me
22	*i-Pr*	$BocNHCH_2CH_2NHCH_2CONH$	Me
23	*i-Pr*	$HOCH_2CH(CH_3)NHCH_2CONH$	Me
24	*i-Pr*	$CH_3CH(OH)CH_2NHCH_2CONH$	Me
25	*i-Pr*	$H_2NCH_2CH_2NHCH_2CONH$	Me

26	*i-Pr*	morpholin-4-ylCH$_2$CH$_2$NHCH$_2$CONH	Me
27	*i-Pr*	1-CH$_3$-piperidin-4-ylN(CH$_3$)CH$_2$CONH	Me
28	*i-Pr*	(CH$_3$)$_2$NCH$_2$CH$_2$N(CH$_3$)CH$_2$CONH	Me
29	*i-Pr*	(CH$_3$)$_2$NCH(CH$_3$)CONH	Me
30	*i-Pr*	1-CH$_3$-L-prolylNH	Me
31	*i-Pr*	Homopiperazin-1-ylCH$_2$CONH	Me
32	*i-Pr*	CH$_3$CH$_2$NHCH$_2$CONH	Me
33	*i-Pr*	4-(CH$_2$NH$_2$)piperidin-1-ylCH$_2$CONH	Me
34	*i-Pr*	(CH$_3$)$_2$NCH$_2$CH$_2$NHCH$_2$CONH	Me
35	*i-Pr*	*cyclo*-C$_3$H$_5$NHCH$_2$CONH	Me
36	*i-Pr*	Piperidin-4-ylCH$_2$NHCH$_2$CONH	Me
37	i-Pr	HO(CH$_2$)$_3$NHCH$_2$CONH	Me
38	*i-Pr*	1-Bocpiperidin-4-ylCH$_2$NHCH$_2$CONH	Me
39	i-Pr	HOCH$_2$CH$_2$NHCH$_2$CONH	Me
40	*i-Pr*	*cyclo*-C$_4$H$_7$NHCH$_2$CONH	Me
41	*i-Pr*	azetidin-3-ylCONH	Me
42	*i-Pr*	D-prolylNH·HCl	Me
43	*i-Pr*	Boc-D-prolylNH	Me
44	*i-Pr*	L-prolylNH·HCl	Me
45	*i-Pr*	Boc-L-prolylNH	Me
46	*i-Pr*	piperidin-1-ylCH$_2$CH$_2$NHCH$_2$CONH	Me
47	*i-Pr*	(CH$_3$)$_2$CHNHCH$_2$CONH	Me
48	*i-Pr*	BocNHCH$_2$CH$_2$CONH	Me
49	*i-Pr*	piperazin-2-yl-CONH	Me
50	*i-Pr*	4-Me-piperazin-2-yl-CONH	Me
51	*i-Pr*	piperidin-1-ylNHCONH	Me
52	*i-Pr*	H$_2$NCH$_2$CH$_2$NHCONH·F$_3$CCO$_2$H	Me
53	*i-Pr*	pyrid-2-ylNHCONH	Me
54	*i-Pr*	(CH$_3$)$_2$NCH$_2$CH$_2$NHCONH	Me
55	*i-Pr*	BocNHCH$_2$CH$_2$NHCONH	Me
56	*i-Pr*	HO(CH$_2$)$_4$NHCONH	Me
57	*i-Pr*	(CH$_3$)$_2$NNHCONH	Me
58	*i-Pr*	(CH$_3$)$_2$N(CH$_2$)$_3$NHCONH	Me
59	*i-Pr*	1-CH$_3$-homopiperazin-4-yl-CONH	Me
60	*i-Pr*	CH$_3$SO$_2$NHCONH	Me
61	*i-Pr*	CH$_3$ONHCONH	Me
62	*i-Pr*	(CH$_3$)$_2$NCH$_2$CH$_2$NHCONH	Me

63	*i-Pr*	1-CH_3-piperidin-4-ylN(CH_3)CONH	Me
64	*i-Pr*	Tetrahydrofur-2-ylCH_2NHCONH	Me
65	*i-Pr*	$CH_3(CH_2)_2CH(OH)CH_2$NHCONH	Me
66	*i-Pr*	$HOCH_2CH(CH_3)$NHCONH	Me
67	*i-Pr*	$CH_3CH(OH)CH_2$NHCONH	Me
68	*i-Pr*	$HOCH_2CH_2$NHCONH	Me
69	*i-Pr*	morpholin-4-ylNHCONH	Me
70	*i-Pr*	$(CH_3)_2NCH(CH_3)CH_2$NHCONH	Me
71	*i-Pr*	1-CH_3-piperazin-4-ylNHCONH	Me
72	*i-Pr*	morpholin-4-ylCH_2CH_2NHCONH	Me
73	*i-Pr*	1-CH_3-piperazin-4-ylCONH	Me
74	*i-Pr*	pyrid-2-ylNHCONH	Me
75	*i-Pr*	pyrid-4-ylNHCONH	Me
76	i-Pr	Pyrrolidin-1-yl$CH_2CH_2NHCH_2$CONH	Me
77	i-Pr	2-CH_3-piperazin-1-ylCONH	Me
78	i-Pr	3-CH_3-piperazin-1-ylCH_2CONH	Me
79	i-Pr	trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH	Me
80	i-Pr	cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH	Me
81	i-Pr	cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH	Me
82	i-Pr	trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH	Me
83	i-Pr	trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH	Me
84	i-Pr	(R)-1-Ethylpyrrolidin-2-ylCH_2NHCONH	Me
85	i-Pr	(S)-1-Ethylpyrrolidin-2-ylCH_2NHCONH	Me
86	i-Pr	5-CH_3-pyrazin-2-ylCH_2NHCH_2CONH	Me

Table XVIII



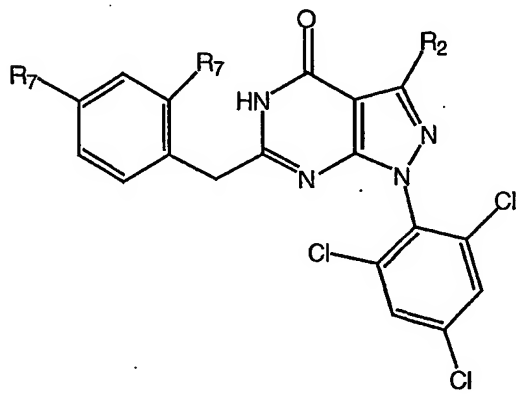
Ex. #	R^2	R^7(meta)	R^7(ortho)

1	*i-Pr*	1-CH_3-piperazin-4-ylCH_2CONH	Me
2	*i-Pr*	$CH_3NHCONH$	Me
3	*i-Pr*	morpholin-4-ylCH_2CONH	Me
4	*i-Pr*	azetidin-1-ylCH_2CONH	Me
5	*i-Pr*	$(CH_3)_2NCH_2CH_2SO_2NH$	Me
6	*i-Pr*	$EtO_2CCH_2NHCONH$	Me
7	*i-Pr*	Hydantoin-1-yl	Me
8	*i-Pr*	$HOCH_2CH_2NHCONH$	Me
9	*i-Pr*	$HO_2C(CH_2)_2CONH$	Me
10	*i-Pr*	imidazol-1-ylCH_2CONH	Me
11	*i-Pr*	Morpholin-4-yl$CH_2CH_2NHCSNH$	Me
12	*i-Pr*	$HO_2CCH_2NHCONH$	Me
13	*i-Pr*	$HO_2C(CH_2)_3CONH$	Me
14	*i-Pr*	H_2NCH_2CONH	Me
15	*i-Pr*	CH_3NHCH_2CONH	Me
16	*i-Pr*	4-F-phenylCH_2NHCH_2CONH	Me
17	*i-Pr*	pyrrolidin-1-ylCH_2CONH	Me
18	*i-Pr*	pyrid-2-ylCH_2NHCH_2CONH	Me
19	*i-Pr*	pyrid-3-ylCH_2NHCH_2CONH	Me
20	*i-Pr*	pyrid-4-ylCH_2NHCH_2CONH	Me
21	*i-Pr*	$BocNHCH_2CH_2NHCH_2CONH$	Me
22	*i-Pr*	$HOCH_2CH(CH_3)NHCH_2CONH$	Me
23	*i-Pr*	$CH_3CH(OH)CH_2NHCH_2CONH$	Me
24	*i-Pr*	$H_2NCH_2CH_2NHCH_2CONH$	Me
25	*i-Pr*	morpholin-4-yl$CH_2CH_2NHCH_2CONH$	Me
26	*i-Pr*	1-CH_3-piperidin-4-yl$N(CH_3)CH_2CONH$	Me
27	*i-Pr*	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$	Me
28	*i-Pr*	$(CH_3)_2NCH(CH_3)CONH$	Me
29	*i-Pr*	1-CH_3-L-prolylNH	Me
30	*i-Pr*	Homopiperazin-1-ylCH_2CONH	Me
31	*i-Pr*	$CH_3CH_2NHCH_2CONH$	Me
32	*i-Pr*	4-(CH_2NH_2)piperidin-1-ylCH_2CONH	Me
33	*i-Pr*	$(CH_3)_2NCH_2CH_2NHCH_2CONH$	Me
34	*i-Pr*	*cyclo*-$C_3H_5NHCH_2CONH$	Me
35	*i-Pr*	Piperidin-4-ylCH_2NHCH_2CONH	Me
36	i-Pr	$HO(CH_2)_3NHCH_2CONH$	Me
37	*i-Pr*	1-Bocpiperidin-4-ylCH_2NHCH_2CONH	Me

38	i-Pr	$HOCH_2CH_2NHCH_2CONH$	Me
39	*i-Pr*	*cyclo*-$C_4H_7NHCH_2CONH$	Me
40	*i-Pr*	azetidin-3-ylCONH	Me
41	*i-Pr*	D-prolylNH·HCl	Me
42	*i-Pr*	Boc-D-prolylNH	Me
43	*i-Pr*	L-prolylNH·HCl	Me
44	*i-Pr*	Boc-L-prolylNH	Me
45	*i-Pr*	piperidin-1-yl$CH_2CH_2NHCH_2CONH$	Me
46	*i-Pr*	$(CH_3)_2CHNHCH_2CONH$	Me
47	*i-Pr*	$BocNHCH_2CH_2CONH$	Me
48	*i-Pr*	piperazin-2-yl-CONH	Me
49	*i-Pr*	4-Me-piperazin-2-yl-CONH	Me
50	*i-Pr*	piperidin-1-ylNHCONH	Me
51	*i-Pr*	$H_2NCH_2CH_2NHCONH·F_3CCO_2H$	Me
52	*i-Pr*	pyrid-2-ylNHCONH	Me
53	*i-Pr*	$(CH_3)_2NCH_2CH_2NHCONH$	Me
54	*i-Pr*	$BocNHCH_2CH_2NHCONH$	Me
55	*i-Pr*	$HO(CH_2)_4NHCONH$	Me
56	*i-Pr*	$(CH_3)_2NNHCONH$	Me
57	*i-Pr*	$(CH_3)_2N(CH_2)_3NHCONH$	Me
58	*i-Pr*	1-CH_3-homopiperazin-4-yl-CONH	Me
59	*i-Pr*	$CH_3SO_2NHCONH$	Me
60	*i-Pr*	$CH_3ONHCONH$	Me
61	*i-Pr*	$(CH_3)_2NCH_2CH_2NHCONH$	Me
62	*i-Pr*	1-CH_3-piperidin-4-ylN(CH_3)CONH	Me
63	*i-Pr*	tetrahydrofur-2-yl$CH_2NHCONH$	Me
64	*i-Pr*	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$	Me
65	*i-Pr*	$HOCH_2CH(CH_3)NHCONH$	Me
66	*i-Pr*	$CH_3CH(OH)CH_2NHCONH$	Me
67	*i-Pr*	$HOCH_2CH_2NHCONH$	Me
68	*i-Pr*	morpholin-4-ylNHCONH	Me
69	*i-Pr*	$(CH_3)_2NCH(CH_3)CH_2NHCONH$	Me
70	*i-Pr*	1-CH_3-piperazin-4-ylNHCONH	Me
71	*i-Pr*	morpholin-4-yl$CH_2CH_2NHCONH$	Me
72	*i-Pr*	1-CH_3-piperazin-4-ylCONH	Me
73	*i-Pr*	pyrid-2-ylNHCONH	Me
74	*i-Pr*	pyrid-4-ylNHCONH	Me

75	i-Pr	pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$	Me
76	i-Pr	2-CH_3-piperazin-1-ylCONH	Me
77	i-Pr	3-CH_3-piperazin-1-ylCH_2CONH	Me
78	i-Pr	trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH	Me
79	i-Pr	cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH	Me
80	i-Pr	cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH	Me
81	i-Pr	trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH	Me
82	i-Pr	trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH	Me
83	i-Pr	(R)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$	Me
84	i-Pr	(S)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$	Me
85	i-Pr	5-CH_3-pyrazin-2-ylCH_2NHCH_2CONH	Me

Table XIX

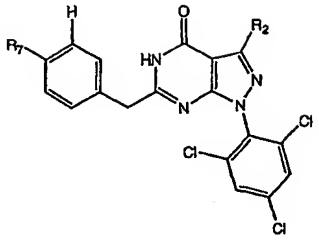


Ex.#	R^2	R^7(para)	R^7(ortho)
1	*i-Pr*	$(CH_3)_2NCH_2CONH$	Me
2	*i-Pr*	1-CH_3-piperazin-4-ylCH_2CONH	Me
3	*i-Pr*	$CH_3NHCONH$	Me
4	*i-Pr*	Morpholin-4-ylCH_2CONH	Me
5	*i-Pr*	Azetidin-1-ylCH_2CONH	Me
6	*i-Pr*	$(CH_3)_2NCH_2CH_2SO_2NH$	Me
7	*i-Pr*	$EtO_2CCH_2NHCONH$	Me
8	*i-Pr*	Hydantoin-1-yl	Me
9	*i-Pr*	$HOCH_2CH_2NHCONH$	Me
10	*i-Pr*	$HO_2C(CH_2)_2CONH$	Me
11	*i-Pr*	Imidazol-1-ylCH_2CONH	Me
12	*i-Pr*	Morpholin-4-yl$CH_2CH_2NHCSNH$	Me
13	*i-Pr*	$HO_2CCH_2NHCONH$	Me

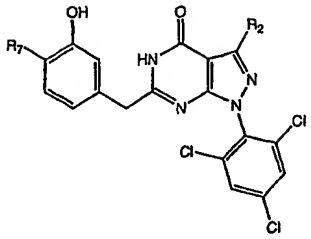
14	*i-Pr*	$HO_2C(CH_2)_3CONH$	Me
15	*i-Pr*	H_2NCH_2CONH	Me
16	*i-Pr*	CH_3NHCH_2CONH	Me
17	*i-Pr*	4-F-phenylCH_2NHCH_2CONH	Me
18	*i-Pr*	pyrrolidin-1-ylCH_2CONH	Me
19	*i-Pr*	pyrid-2-ylCH_2NHCH_2CONH	Me
20	*i-Pr*	pyrid-3-ylCH_2NHCH_2CONH	Me
21	*i-Pr*	pyrid-4-ylCH_2NHCH_2CONH	Me
22	*i-Pr*	$BocNHCH_2CH_2NHCH_2CONH$	Me
23	*i-Pr*	$HOCH_2CH(CH_3)NHCH_2CONH$	Me
24	*i-Pr*	$CH_3CH(OH)CH_2NHCH_2CONH$	Me
25	*i-Pr*	$H_2NCH_2CH_2NHCH_2CONH$	Me
26	*i-Pr*	morpholin-4-yl$CH_2CH_2NHCH_2CONH$	Me
27	*i-Pr*	1-CH_3-piperidin-4-yl$N(CH_3)CH_2CONH$	Me
28	*i-Pr*	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$	Me
29	*i-Pr*	$(CH_3)_2NCH(CH_3)CONH$	Me
30	*i-Pr*	1-CH_3-L-prolylNH	Me
31	*i-Pr*	Homopiperazin-1-ylCH_2CONH	Me
32	*i-Pr*	$CH_3CH_2NHCH_2CONH$	Me
33	*i-Pr*	4-(CH_2NH_2)piperidin-1-ylCH_2CONH	Me
34	*i-Pr*	$(CH_3)_2NCH_2CH_2NHCH_2CONH$	Me
35	*i-Pr*	*cyclo*-$C_3H_5NHCH_2CONH$	Me
36	*i-Pr*	Piperidin-4-ylCH_2NHCH_2CONH	Me
37	i-Pr	$HO(CH_2)_3NHCH_2CONH$	Me
38	*i-Pr*	1-Bocpiperidin-4-ylCH_2NHCH_2CONH	Me
39	i-Pr	$HOCH_2CH_2NHCH_2CONH$	Me
40	*i-Pr*	*cyclo*-$C_4H_7NHCH_2CONH$	Me
41	*i-Pr*	azetidin-3-ylCONH	Me
42	*i-Pr*	D-prolylNH·HCl	Me
43	*i-Pr*	Boc-D-prolylNH	Me
44	*i-Pr*	L-prolylNH·HCl	Me
45	*i-Pr*	Boc-L-prolylNH	Me
46	*i-Pr*	piperidin-1-yl$CH_2CH_2NHCH_2CONH$	Me
47	*i-Pr*	$(CH_3)_2CHNHCH_2CONH$	Me
48	*i-Pr*	$BocNHCH_2CH_2CONH$	Me
49	*i-Pr*	piperazin-2-yl-CONH	Me
50	*i-Pr*	4-Me-piperazin-2-yl-CONH	Me

51	*i-Pr*	piperidin-1-ylNHCONH	Me
52	*i-Pr*	$H_2NCH_2CH_2NHCONH \cdot F_3CCO_2H$	Me
53	*i-Pr*	pyrid-2-ylNHCONH	Me
54	*i-Pr*	$(CH_3)_2NCH_2CH_2NHCONH$	Me
55	*i-Pr*	$BocNHCH_2CH_2NHCONH$	Me
56	*i-Pr*	$HO(CH_2)_4NHCONH$	Me
57	*i-Pr*	$(CH_3)_2NNHCONH$	Me
58	*i-Pr*	$(CH_3)_2N(CH_2)_3NHCONH$	Me
59	*i-Pr*	$1\text{-}CH_3$-homopiperazin-4-yl-CONH	Me
60	*i-Pr*	$CH_3SO_2NHCONH$	Me
61	*i-Pr*	$CH_3ONHCONH$	Me
62	*i-Pr*	$(CH_3)_2NCH_2CH_2NHCONH$	Me
63	*i-Pr*	$1\text{-}CH_3$-piperidin-4-ylN(CH_3)CONH	Me
64	*i-Pr*	tetrahydrofur-2-yl$CH_2NHCONH$	Me
65	*i-Pr*	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$	Me
66	*i-Pr*	$HOCH_2CH(CH_3)NHCONH$	Me
67	*i-Pr*	$CH_3CH(OH)CH_2NHCONH$	Me
68	*i-Pr*	$HOCH_2CH_2NHCONH$	Me
69	*i-Pr*	morpholin-4-ylNHCONH	Me
70	*i-Pr*	$(CH_3)_2NCH(CH_3)CH_2NHCONH$	Me
71	*i-Pr*	$1\text{-}CH_3$-piperazin-4-ylNHCONH	Me
72	*i-Pr*	morpholin-4-yl$CH_2CH_2NHCONH$	Me
73	*i-Pr*	$1\text{-}CH_3$-piperazin-4-ylCONH	Me
74	*i-Pr*	pyrid-2-ylNHCONH	Me
75	*i-Pr*	pyrid-4-ylNHCONH	Me
76	i-Pr	pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$	Me
77	i-Pr	$2\text{-}CH_3$-piperazin-1-ylCONH	Me
78	i-Pr	$3\text{-}CH_3$-piperazin-1-ylCH_2CONH	Me
79	i-Pr	trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH	Me
80	i-Pr	cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH	Me
81	i-Pr	cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH	Me
82	i-Pr	trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH	Me
83	i-Pr	trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH	Me
84	i-Pr	(R)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$	Me
85	i-Pr	(S)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$	Me
86	i-Pr	$5\text{-}CH_3$-pyrazin-2-ylCH_2NHCH_2CONH	Me

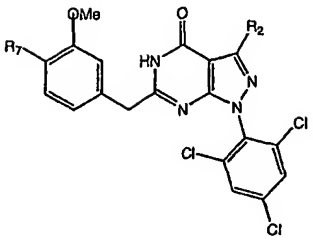
Table XX



(a)



(b)



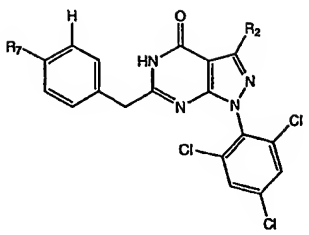
(c)

Ex.#	R^2	R^7
1	Et	1-CH_3-piperazin-4-ylCH_2CONH
2	Et	$CH_3NHCONH$
3	Et	Morpholin-4-ylCH_2CONH
4	Et	Azetidin-1-ylCH_2CONH
5	Et	$(CH_3)_2NCH_2CH_2SO_2NH$
6	Et	$EtO_2CCH_2NHCONH$
7	Et	Hydantoin-1-yl
8	Et	$HOCH_2CH_2NHCONH$
9	Et	$HO_2C(CH_2)_2CONH$
10	Et	Imidazol-1-ylCH_2CONH
11	Et	Morpholin-4-yl$CH_2CH_2NHCSNH$
12	Et	$HO_2CCH_2NHCONH$
13	Et	$HO_2C(CH_2)_3CONH$
14	Et	H_2NCH_2CONH
15	Et	CH_3NHCH_2CONH
16	Et	4-F-phenylCH_2NHCH_2CONH
17	Et	pyrrolidin-1-ylCH_2CONH
18	Et	pyrid-2-ylCH_2NHCH_2CONH
19	Et	pyrid-3-ylCH_2NHCH_2CONH
20	Et	pyrid-4-ylCH_2NHCH_2CONH
21	Et	$BocNHCH_2CH_2NHCH_2CONH$
22	Et	$HOCH_2CH(CH_3)NHCH_2CONH$
23	Et	$CH_3CH(OH)CH_2NHCH_2CONH$
24	Et	$H_2NCH_2CH_2NHCH_2CONH$
25	Et	morpholin-4-yl$CH_2CH_2NHCH_2CONH$
26	Et	1-CH_3-piperidin-4-yl$N(CH_3)CH_2CONH$

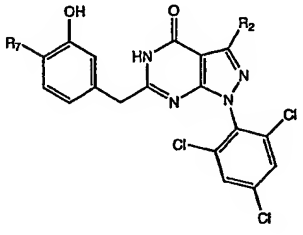
27	Et	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$
28	Et	$(CH_3)_2NCH(CH_3)CONH$
29	Et	1-CH_3-L-prolylNH
30	Et	Homopiperazin-1-ylCH_2CONH
31	Et	$CH_3CH_2NHCH_2CONH$
32	Et	4-(CH_2NH_2)piperidin-1-ylCH_2CONH
33	Et	$(CH_3)_2NCH_2CH_2NHCH_2CONH$
34	Et	*cyclo*-$C_3H_5NHCH_2CONH$
35	Et	Piperidin-4-ylCH_2NHCH_2CONH
36	Et	$HO(CH_2)_3NHCH_2CONH$
37	Et	1-Bocpiperidin-4-ylCH_2NHCH_2CONH
38	Et	$HOCH_2CH_2NHCH_2CONH$
39	Et	*cyclo*-$C_4H_7NHCH_2CONH$
40	Et	azetidin-3-ylCONH
41	Et	D-prolylNH·HCl
42	Et	Boc-D-prolylNH
43	Et	L-prolylNH·HCl
44	Et	Boc-L-prolylNH
45	Et	piperidin-1-yl$CH_2CH_2NHCH_2CONH$
46	Et	$(CH_3)_2CHNHCH_2CONH$
47	Et	$BocNHCH_2CH_2CONH$
48	Et	piperazin-2-yl-CONH
49	Et	4-Me-piperazin-2-yl-CONH
50	Et	piperidin-1-ylNHCONH
51	Et	$H_2NCH_2CH_2NHCONH·F_3CCO_2H$
52	Et	pyrid-2-ylNHCONH
53	Et	$(CH_3)_2NCH_2CH_2NHCONH$
54	Et	$BocNHCH_2CH_2NHCONH$
55	Et	$HO(CH_2)_4NHCONH$
56	Et	$(CH_3)_2NNHCONH$
57	Et	$(CH_3)_2N(CH_2)_3NHCONH$
58	Et	1-CH_3-homopiperazin-4-yl-CONH
59	Et	$CH_3SO_2NHCONH$
60	Et	$CH_3ONHCONH$
61	Et	$(CH_3)_2NCH_2CH_2NHCONH$
62	Et	1-CH_3-piperidin-4-yl$N(CH_3)CONH$
63	Et	Tetrahydrofur-2-yl$CH_2NHCONH$

64	Et	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$
65	Et	$HOCH_2CH(CH_3)NHCONH$
66	Et	$CH_3CH(OH)CH_2NHCONH$
67	Et	$HOCH_2CH_2NHCONH$
68	Et	morpholin-4-ylNHCONH
69	Et	$(CH_3)_2NCH(CH_3)CH_2NHCONH$
70	Et	1-CH_3-piperazin-4-ylNHCONH
71	Et	morpholin-4-yl$CH_2CH_2NHCONH$
72	Et	1-CH_3-piperazin-4-ylCONH
73	Et	pyrid-2-ylNHCONH
74	Et	pyrid-4-ylNHCONH
75	Et	pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$
76	Et	2-CH_3-piperazin-1-ylCONH
77	Et	3-CH_3-piperazin-1-ylCH_2CONH
78	Et	trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH
79	Et	cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH
80	Et	cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH
81	Et	trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH
82	Et	trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH
83	Et	(R)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
84	Et	(S)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
85	Et	5-CH_3-pyrazin-2-ylCH_2NHCH_2CONH

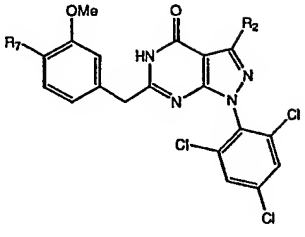
Table XXI



(a)



(b)



(c)

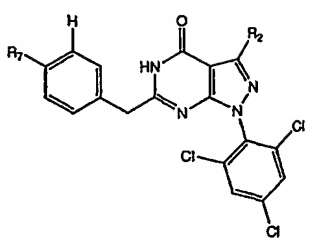
Ex.#	R^2	R^7
1	cyc-Pr	1-CH_3-piperazin-4-ylCH_2CONH
2	cyc-Pr	$CH_3NHCONH$
3	cyc-Pr	Morpholin-4-ylCH_2CONH

4	cyc-Pr	Azetidin-1-ylCH_2CONH
5	cyc-Pr	$(CH_3)_2NCH_2CH_2SO_2NH$
6	cyc-Pr	$EtO_2CCH_2NHCONH$
7	cyc-Pr	Hydantoin-1-yl
8	cyc-Pr	$HOCH_2CH_2NHCONH$
9	cyc-Pr	$HO_2C(CH_2)_2CONH$
10	cyc-Pr	imidazol-1-ylCH_2CONH
11	cyc-Pr	Morpholin-4-yl$CH_2CH_2NHCSNH$
12	cyc-Pr	$HO_2CCH_2NHCONH$
13	cyc-Pr	$HO_2C(CH_2)_3CONH$
14	cyc-Pr	H_2NCH_2CONH
15	cyc-Pr	CH_3NHCH_2CONH
16	cyc-Pr	4-F-phenylCH_2NHCH_2CONH
17	cyc-Pr	pyrrolidin-1-ylCH_2CONH
18	cyc-Pr	pyrid-2-ylCH_2NHCH_2CONH
19	cyc-Pr	pyrid-3-ylCH_2NHCH_2CONH
20	cyc-Pr	pyrid-4-ylCH_2NHCH_2CONH
21	cyc-Pr	Boc$NHCH_2CH_2NHCH_2CONH$
22	cyc-Pr	$HOCH_2CH(CH_3)NHCH_2CONH$
23	cyc-Pr	$CH_3CH(OH)CH_2NHCH_2CONH$
24	cyc-Pr	$H_2NCH_2CH_2NHCH_2CONH$
25	cyc-Pr	morpholin-4-yl$CH_2CH_2NHCH_2CONH$
26	cyc-Pr	1-CH_3-piperidin-4-yl$N(CH_3)CH_2CONH$
27	cyc-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$
28	cyc-Pr	$(CH_3)_2NCH(CH_3)CONH$
29	cyc-Pr	1-CH_3-L-prolylNH
30	cyc-Pr	Homopiperazin-1-ylCH_2CONH
31	cyc-Pr	$CH_3CH_2NHCH_2CONH$
32	cyc-Pr	4-(CH_2NH_2)piperidin-1-ylCH_2CONH
33	cyc-Pr	$(CH_3)_2NCH_2CH_2NHCH_2CONH$
34	cyc-Pr	*cyclo*-$C_3H_5NHCH_2CONH$
35	cyc-Pr	Piperidin-4-ylCH_2NHCH_2CONH
36	cyc-Pr	$HO(CH_2)_3NHCH_2CONH$
37	cyc-Pr	1-Bocpiperidin-4-ylCH_2NHCH_2CONH
38	cyc-Pr	$HOCH_2CH_2NHCH_2CONH$
39	cyc-Pr	*cyclo*-$C_4H_7NHCH_2CONH$
40	cyc-Pr	azetidin-3-ylCONH

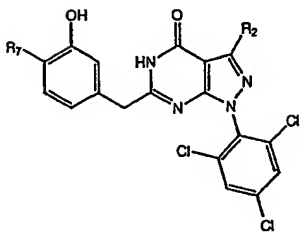
41	cyc-Pr	D-prolylNH·HCl
42	cyc-Pr	Boc-D-prolylNH
43	cyc-Pr	L-prolylNH·HCl
44	cyc-Pr	Boc-L-prolylNH
45	cyc-Pr	piperidin-1-yl$CH_2CH_2NHCH_2CONH$
46	cyc-Pr	$(CH_3)_2CHNHCH_2CONH$
47	cyc-Pr	$BocNHCH_2CH_2CONH$
48	cyc-Pr	piperazin-2-yl-CONH
49	cyc-Pr	4-Me-piperazin-2-yl-CONH
50	cyc-Pr	piperidin-1-ylNHCONH
51	cyc-Pr	$H_2NCH_2CH_2NHCONH·F_3CCO_2H$
52	cyc-Pr	pyrid-2-ylNHCONH
53	cyc-Pr	$(CH_3)_2NCH_2CH_2NHCONH$
54	cyc-Pr	$BocNHCH_2CH_2NHCONH$
55	cyc-Pr	$HO(CH_2)_4NHCONH$
56	cyc-Pr	$(CH_3)_2NNHCONH$
57	cyc-Pr	$(CH_3)_2N(CH_2)_3NHCONH$
58	cyc-Pr	1-CH_3-homopiperazin-4-yl-CONH
59	cyc-Pr	$CH_3SO_2NHCONH$
60	cyc-Pr	$CH_3ONHCONH$
61	cyc-Pr	$(CH_3)_2NCH_2CH_2NHCONH$
62	cyc-Pr	1-CH_3-piperidin-4-ylN(CH_3)CONH
63	cyc-Pr	tetrahydrofur-2-yl$CH_2NHCONH$
64	cyc-Pr	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$
65	cyc-Pr	$HOCH_2CH(CH_3)NHCONH$
66	cyc-Pr	$CH_3CH(OH)CH_2NHCONH$
67	cyc-Pr	$HOCH_2CH_2NHCONH$
68	cyc-Pr	morpholin-4-ylNHCONH
69	cyc-Pr	$(CH_3)_2NCH(CH_3)CH_2NHCONH$
70	cyc-Pr	1-CH_3-piperazin-4-ylNHCONH
71	cyc-Pr	morpholin-4-yl$CH_2CH_2NHCONH$
72	cyc-Pr	1-CH_3-piperazin-4-ylCONH
73	cyc-Pr	pyrid-2-ylNHCONH
74	cyc-Pr	pyrid-4-ylNHCONH
75	cyc-Pr	pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$
76	cyc-Pr	2-CH_3-piperazin-1-ylCONH
77	cyc-Pr	3-CH_3-piperazin-1-ylCH_2CONH

78	cyc-Pr	trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH
79	cyc-Pr	cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH
80	cyc-Pr	cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH
81	cyc-Pr	trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH
82	cyc-Pr	trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH
83	cyc-Pr	(R)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
84	cyc-Pr	(S)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
85	cyc-Pr	5-CH_3-pyrazin-2-ylCH_2NHCH_2CONH

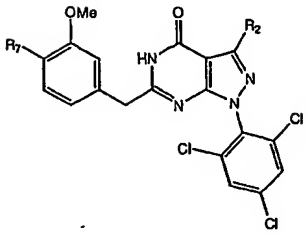
Table XXII



(a)



(b)



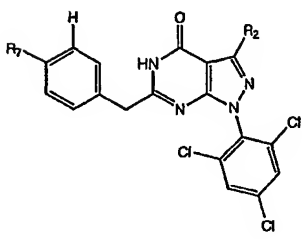
(c)

Ex. #	R^2	R^7
1	1-Methylcyc-Pr	1-CH_3-piperazin-4-ylCH_2CONH
2	1-Methylcyc-Pr	$CH_3NHCONH$
3	1-Methylcyc-Pr	Morpholin-4-ylCH_2CONH
4	1-Methylcyc-Pr	Azetidin-1-ylCH_2CONH
5	1-Methylcyc-Pr	$(CH_3)_2NCH_2CH_2SO_2NH$
6	1-Methylcyc-Pr	$EtO_2CCH_2NHCONH$
7	1-Methylcyc-Pr	Hydantoin-1-yl
8	1-Methylcyc-Pr	$HOCH_2CH_2NHCONH$
9	1-Methylcyc-Pr	$HO_2C(CH_2)_2CONH$
10	1-Methylcyc-Pr	Imidazol-1-ylCH_2CONH
11	1-Methylcyc-Pr	Morpholin-4-yl$CH_2CH_2NHCSNH$
12	1-Methylcyc-Pr	$HO_2CCH_2NHCONH$
13	1-Methylcyc-Pr	$HO_2C(CH_2)_3CONH$
14	1-Methylcyc-Pr	H_2NCH_2CONH
15	1-Methylcyc-Pr	CH_3NHCH_2CONH
16	1-Methylcyc-Pr	4-F-phenylCH_2NHCH_2CONH
17	1-Methylcyc-Pr	Pyrrolidin-1-ylCH_2CONH
18	1-Methylcyc-Pr	Pyrid-2-ylCH_2NHCH_2CONH
19	1-Methylcyc-Pr	Pyrid-3-ylCH_2NHCH_2CONH
20	1-Methylcyc-Pr	Pyrid-4-ylCH_2NHCH_2CONH
21	1-Methylcyc-Pr	$BocNHCH_2CH_2NHCH_2CONH$
22	1-Methylcyc-Pr	$HOCH_2CH(CH_3)NHCH_2CONH$
23	1-Methylcyc-Pr	$CH_3CH(OH)CH_2NHCH_2CONH$
24	1-Methylcyc-Pr	$H_2NCH_2CH_2NHCH_2CONH$
25	1-Methylcyc-Pr	Morpholin-4-yl$CH_2CH_2NHCH_2CONH$
26	1-Methylcyc-Pr	1-CH_3-piperidin-4-yl$N(CH_3)CH_2CONH$

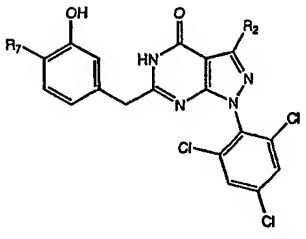
27	1-Methylcyc-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$
28	1-Methylcyc-Pr	$(CH_3)_2NCH(CH_3)CONH$
29	1-Methylcyc-Pr	$1\text{-}CH_3\text{-}L\text{-}prolylNH$
30	1-Methylcyc-Pr	$Homopiperazin\text{-}1\text{-}ylCH_2CONH$
31	1-Methylcyc-Pr	$CH_3CH_2NHCH_2CONH$
32	1-Methylcyc-Pr	$4\text{-}(CH_2NH_2)piperidin\text{-}1\text{-}ylCH_2CONH$
33	1-Methylcyc-Pr	$(CH_3)_2NCH_2CH_2NHCH_2CONH$
34	1-Methylcyc-Pr	$Cyclo\text{-}C_3H_5NHCH_2CONH$
35	1-Methylcyc-Pr	$Piperidin\text{-}4\text{-}ylCH_2NHCH_2CONH$
36	1-Methylcyc-Pr	$HO(CH_2)_3NHCH_2CONH$
37	1-Methylcyc-Pr	$1\text{-}Bocpiperidin\text{-}4\text{-}ylCH_2NHCH_2CONH$
38	1-Methylcyc-Pr	$HOCH_2CH_2NHCH_2CONH$
39	1-Methylcyc-Pr	$Cyclo\text{-}C_4H_7NHCH_2CONH$
40	1-Methylcyc-Pr	$Azetidin\text{-}3\text{-}ylCONH$
41	1-Methylcyc-Pr	$D\text{-}prolylNH\cdot HCl$
42	1-Methylcyc-Pr	$Boc\text{-}D\text{-}prolylNH$
43	1-Methylcyc-Pr	$L\text{-}prolylNH\cdot HCl$
44	1-Methylcyc-Pr	$Boc\text{-}L\text{-}prolylNH$
45	1-Methylcyc-Pr	$Piperidin\text{-}1\text{-}ylCH_2CH_2NHCH_2CONH$
46	1-Methylcyc-Pr	$(CH_3)_2CHNHCH_2CONH$
47	1-Methylcyc-Pr	$BocNHCH_2CH_2CONH$
48	1-Methylcyc-Pr	$Piperazin\text{-}2\text{-}yl\text{-}CONH$
49	1-Methylcyc-Pr	$4\text{-}Me\text{-}piperazin\text{-}2\text{-}yl\text{-}CONH$
50	1-Methylcyc-Pr	$Piperidin\text{-}1\text{-}ylNHCONH$
51	1-Methylcyc-Pr	$H_2NCH_2CH_2NHCONH\cdot F_3CCO_2H$
52	1-Methylcyc-Pr	$Pyrid\text{-}2\text{-}ylNHCONH$
53	1-Methylcyc-Pr	$(CH_3)_2NCH_2CH_2NHCONH$
54	1-Methylcyc-Pr	$BocNHCH_2CH_2NHCONH$
55	1-Methylcyc-Pr	$HO(CH_2)_4NHCONH$
56	1-Methylcyc-Pr	$(CH_3)_2NNHCONH$
57	1-Methylcyc-Pr	$(CH_3)_2N(CH_2)_3NHCONH$
58	1-Methylcyc-Pr	$1\text{-}CH_3\text{-}homopiperazin\text{-}4\text{-}yl\text{-}CONH$
59	1-Methylcyc-Pr	$CH_3SO_2NHCONH$
60	1-Methylcyc-Pr	$CH_3ONHCONH$
61	1-Methylcyc-Pr	$(CH_3)_2NCH_2CH_2NHCONH$
62	1-Methylcyc-Pr	$1\text{-}CH_3\text{-}piperidin\text{-}4\text{-}ylN(CH_3)CONH$
63	1-Methylcyc-Pr	$Tetrahydrofur\text{-}2\text{-}ylCH_2NHCONH$

64	1-Methylcyc-Pr	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$
65	1-Methylcyc-Pr	$HOCH_2CH(CH_3)NHCONH$
66	1-Methylcyc-Pr	$CH_3CH(OH)CH_2NHCONH$
67	1-Methylcyc-Pr	$HOCH_2CH_2NHCONH$
68	1-Methylcyc-Pr	Morpholin-4-ylNHCONH
69	1-Methylcyc-Pr	$(CH_3)_2NCH(CH_3)CH_2NHCONH$
70	1-Methylcyc-Pr	1-CH_3-piperazin-4-ylNHCONH
71	1-Methylcyc-Pr	Morpholin-4-yl$CH_2CH_2NHCONH$
72	1-Methylcyc-Pr	1-CH_3-piperazin-4-ylCONH
73	1-Methylcyc-Pr	Pyrid-2-ylNHCONH
74	1-Methylcyc-Pr	Pyrid-4-ylNHCONH
75	1-Methylcyc-Pr	Pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$
76	1-Methylcyc-Pr	2-CH_3-piperazin-1-ylCONH
77	1-Methylcyc-Pr	3-CH_3-piperazin-1-ylCH_2CONH
78	1-Methylcyc-Pr	Trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH
79	1-Methylcyc-Pr	Cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH
80	1-Methylcyc-Pr	Cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH
81	1-Methylcyc-Pr	Trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH
82	1-Methylcyc-Pr	Trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH
83	1-Methylcyc-Pr	(R)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
84	1-Methylcyc-Pr	(S)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
85	1-Methylcyc-Pr	5-CH_3-pyrazin-2-ylCH_2NHCH_2CONH

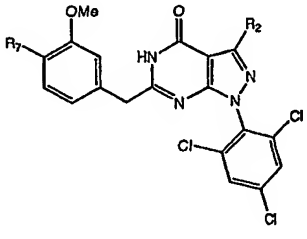
Table XXIII



(a)



(b)



(c)

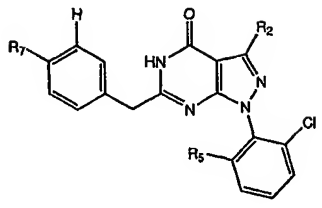
Ex.#	R^2	R^7
1	i-Bu	1-CH_3-piperazin-4-ylCH_2CONH
2	i-Bu	$CH_3NHCONH$

3	i-Bu	Morpholin-4-ylCH_2CONH
4	i-Bu	Azetidin-1-ylCH_2CONH
5	i-Bu	$(CH_3)_2NCH_2CH_2SO_2NH$
6	i-Bu	$EtO_2CCH_2NHCONH$
7	i-Bu	Hydantoin-1-yl
8	i-Bu	$HOCH_2CH_2NHCONH$
9	i-Bu	$HO_2C(CH_2)_2CONH$
10	i-Bu	Imidazol-1-ylCH_2CONH
11	i-Bu	Morpholin-4-yl$CH_2CH_2NHCSNH$
12	i-Bu	$HO_2CCH_2NHCONH$
13	i-Bu	$HO_2C(CH_2)_3CONH$
14	i-Bu	H_2NCH_2CONH
15	i-Bu	CH_3NHCH_2CONH
16	i-Bu	4-F-phenylCH_2NHCH_2CONH
17	i-Bu	Pyrrolidin-1-ylCH_2CONH
18	i-Bu	pyrid-2-ylCH_2NHCH_2CONH
19	i-Bu	pyrid-3-ylCH_2NHCH_2CONH
20	i-Bu	pyrid-4-ylCH_2NHCH_2CONH
21	i-Bu	$BocNHCH_2CH_2NHCH_2CONH$
22	i-Bu	$HOCH_2CH(CH_3)NHCH_2CONH$
23	i-Bu	$CH_3CH(OH)CH_2NHCH_2CONH$
24	i-Bu	$H_2NCH_2CH_2NHCH_2CONH$
25	i-Bu	Morpholin-4-yl$CH_2CH_2NHCH_2CONH$
26	i-Bu	1-CH_3-piperidin-4-yl$N(CH_3)CH_2CONH$
27	i-Bu	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$
28	i-Bu	$(CH_3)_2NCH(CH_3)CONH$
29	i-Bu	1-CH_3-L-prolylNH
30	i-Bu	Homopiperazin-1-ylCH_2CONH
31	i-Bu	$CH_3CH_2NHCH_2CONH$
32	i-Bu	4-(CH_2NH_2)piperidin-1-ylCH_2CONH
33	i-Bu	$(CH_3)_2NCH_2CH_2NHCH_2CONH$
34	i-Bu	*cyclo*-$C_3H_5NHCH_2CONH$
35	i-Bu	Piperidin-4-ylCH_2NHCH_2CONH
36	i-Bu	$HO(CH_2)_3NHCH_2CONH$
37	i-Bu	1-Bocpiperidin-4-ylCH_2NHCH_2CONH
38	i-Bu	$HOCH_2CH_2NHCH_2CONH$
39	i-Bu	*cyclo*-$C_4H_7NHCH_2CONH$

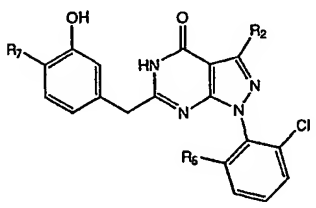
40	i-Bu	azetidin-3-ylCONH
41	i-Bu	D-prolylNH·HCl
42	i-Bu	Boc-D-prolylNH
43	i-Bu	L-prolylNH·HCl
44	i-Bu	Boc-L-prolylNH
45	i-Bu	Piperidin-1-yl$CH_2CH_2NHCH_2CONH$
46	i-Bu	$(CH_3)_2CHNHCH_2CONH$
47	i-Bu	$BocNHCH_2CH_2CONH$
48	i-Bu	Piperazin-2-yl-CONH
49	i-Bu	4-Me-piperazin-2-yl-CONH
50	i-Bu	Piperidin-1-ylNHCONH
51	i-Bu	$H_2NCH_2CH_2NHCONH·F_3CCO_2H$
52	i-Bu	pyrid-2-ylNHCONH
53	i-Bu	$(CH_3)_2NCH_2CH_2NHCONH$
54	i-Bu	$BocNHCH_2CH_2NHCONH$
55	i-Bu	$HO(CH_2)_4NHCONH$
56	i-Bu	$(CH_3)_2NNHCONH$
57	i-Bu	$(CH_3)_2N(CH_2)_3NHCONH$
58	i-Bu	1-CH_3-homopiperazin-4-yl-CONH
59	i-Bu	$CH_3SO_2NHCONH$
60	i-Bu	$CH_3ONHCONH$
61	i-Bu	$(CH_3)_2NCH_2CH_2NHCONH$
62	i-Bu	1-CH_3-piperidin-4-yl$N(CH_3)CONH$
63	i-Bu	Tetrahydrofur-2-yl$CH_2NHCONH$
64	i-Bu	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$
65	i-Bu	$HOCH_2CH(CH_3)NHCONH$
66	i-Bu	$CH_3CH(OH)CH_2NHCONH$
67	i-Bu	$HOCH_2CH_2NHCONH$
68	i-Bu	Morpholin-4-ylNHCONH
69	i-Bu	$(CH_3)_2NCH(CH_3)CH_2NHCONH$
70	i-Bu	1-CH_3-piperazin-4-ylNHCONH
71	i-Bu	Morpholin-4-yl$CH_2CH_2NHCONH$
72	i-Bu	1-CH_3-piperazin-4-ylCONH
73	i-Bu	pyrid-2-ylNHCONH
74	i-Bu	pyrid-4-ylNHCONH
75	i-Bu	Pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$
76	i-Bu	2-CH_3-piperazin-1-ylCONH

77	i-Bu	3-CH_3-piperazin-1-ylCH_2CONH
78	i-Bu	trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH
79	i-Bu	cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH
80	i-Bu	cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH
81	i-Bu	trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH
82	i-Bu	trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH
83	i-Bu	(R)-1-Ethylpyrrolidin-2-ylCH_2NHCONH
84	i-Bu	(S)-1-Ethylpyrrolidin-2-ylCH_2NHCONH
85	i-Bu	5-CH_3-pyrazin-2-ylCH_2NHCH$_2$CONH

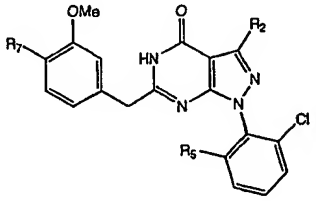
Table XXIV



(a)



(b)



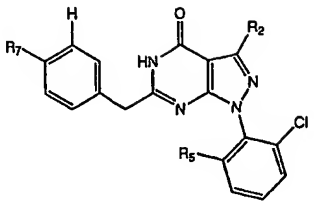
(c)

Ex.#	R^5	R^2	R^7
1	Me	Et	1-CH_3-piperazin-4-ylCH_2CONH
2	Me	Et	CH_3NHCONH
3	Me	Et	Morpholin-4-ylCH_2CONH
4	Me	Et	Azetidin-1-ylCH_2CONH
5	Me	Et	$(CH_3)_2NCH_2CH_2SO_2NH$
6	Me	Et	$EtO_2CCH_2NHCONH$
7	Me	Et	Hydantoin-1-yl
8	Me	Et	$HOCH_2CH_2NHCONH$
9	Me	Et	$HO_2C(CH_2)_2CONH$
10	Me	Et	Imidazol-1-ylCH_2CONH
11	Me	Et	Morpholin-4-ylCH_2CH_2NHCSNH
12	Me	Et	$HO_2CCH_2NHCONH$
13	Me	Et	$HO_2C(CH_2)_3CONH$
14	Me	Et	H_2NCH_2CONH
15	Me	Et	CH_3NHCH_2CONH
16	Me	Et	4-F-phenylCH_2NHCH$_2$CONH
17	Me	Et	Pyrrolidin-1-ylCH_2CONH

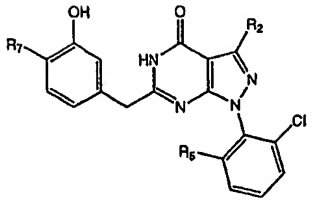
18	Me	Et	Pyrid-2-ylCH_2NHCH_2CONH
19	Me	Et	Pyrid-3-ylCH_2NHCH_2CONH
20	Me	Et	Pyrid-4-ylCH_2NHCH_2CONH
21	Me	Et	$BocNHCH_2CH_2NHCH_2CONH$
22	Me	Et	$HOCH_2CH(CH_3)NHCH_2CONH$
23	Me	Et	$CH_3CH(OH)CH_2NHCH_2CONH$
24	Me	Et	$H_2NCH_2CH_2NHCH_2CONH$
25	Me	Et	Morpholin-4-yl$CH_2CH_2NHCH_2CONH$
26	Me	Et	1-CH_3-piperidin-4-yl$N(CH_3)CH_2CONH$
27	Me	Et	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$
28	Me	Et	$(CH_3)_2NCH(CH_3)CONH$
29	Me	Et	1-CH_3-L-prolylNH
30	Me	Et	Homopiperazin-1-ylCH_2CONH
31	Me	Et	$CH_3CH_2NHCH_2CONH$
32	Me	Et	4-(CH_2NH_2)piperidin-1-ylCH_2CONH
33	Me	Et	$(CH_3)_2NCH_2CH_2NHCH_2CONH$
34	Me	Et	*Cyclo*-$C_3H_5NHCH_2CONH$
35	Me	Et	Piperidin-4-ylCH_2NHCH_2CONH
36	Me	ET	$HO(CH_2)_3NHCH_2CONH$
37	Me	Et	1-Bocpiperidin-4-ylCH_2NHCH_2CONH
38	Me	ET	$HOCH_2CH_2NHCH_2CONH$
39	Me	Et	*Cyclo*-$C_4H_7NHCH_2CONH$
40	Me	Et	Azetidin-3-ylCONH
41	Me	Et	D-prolylNH·HCl
42	Me	Et	Boc-D-prolylNH
43	Me	Et	L-prolylNH·HCl
44	Me	Et	Boc-L-prolylNH
45	Me	Et	Piperidin-1-yl$CH_2CH_2NHCH_2CONH$
46	Me	Et	$(CH_3)_2CHNHCH_2CONH$
47	Me	Et	$BocNHCH_2CH_2CONH$
48	Me	Et	Piperazin-2-yl-CONH
49	Me	Et	4-Me-piperazin-2-yl-CONH
50	Me	Et	Piperidin-1-ylNHCONH
51	Me	Et	$H_2NCH_2CH_2NHCONH·F_3CCO_2H$
52	Me	Et	Pyrid-2-ylNHCONH
53	Me	Et	$(CH_3)_2NCH_2CH_2NHCONH$
54	Me	Et	$BocNHCH_2CH_2NHCONH$

55	Me	Et	$HO(CH_2)_4NHCONH$
56	Me	Et	$(CH_3)_2NNHCONH$
57	Me	Et	$(CH_3)_2N(CH_2)_3NHCONH$
58	Me	Et	$1\text{-}CH_3\text{-homopiperazin-4-yl-CONH}$
59	Me	Et	$CH_3SO_2NHCONH$
60	Me	Et	$CH_3ONHCONH$
61	Me	Et	$(CH_3)_2NCH_2CH_2NHCONH$
62	Me	Et	$1\text{-}CH_3\text{-piperidin-4-ylN}(CH_3)CONH$
63	Me	Et	$Tetrahydrofur\text{-}2\text{-yl}CH_2NHCONH$
64	Me	Et	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$
65	Me	Et	$HOCH_2CH(CH_3)NHCONH$
66	Me	Et	$CH_3CH(OH)CH_2NHCONH$
67	Me	Et	$HOCH_2CH_2NHCONH$
68	Me	Et	$Morpholin\text{-}4\text{-ylNHCONH}$
69	Me	Et	$(CH_3)_2NCH(CH_3)CH_2NHCONH$
70	Me	Et	$1\text{-}CH_3\text{-piperazin-4-ylNHCONH}$
71	Me	Et	$Morpholin\text{-}4\text{-yl}CH_2CH_2NHCONH$
72	Me	Et	$1\text{-}CH_3\text{-piperazin-4-ylCONH}$
73	Me	Et	$Pyrid\text{-}2\text{-ylNHCONH}$
74	Me	Et	$Pyrid\text{-}4\text{-ylNHCONH}$
75	Me	Et	$Pyrrolidin\text{-}1\text{-yl}CH_2CH_2NHCH_2CONH$
76	Me	Et	$2\text{-}CH_3\text{-piperazin-1-ylCONH}$
77	Me	Et	$3\text{-}CH_3\text{-piperazin-1-yl}CH_2CONH$
78	Me	Et	$Trans\text{-}2,5\text{-di-}CH_3\text{-piperazin-1-yl}CH_2CONH$
79	Me	Et	$cis\text{-}2,6\text{-di-}CH_3\text{-piperazin-1-yl}CH_2CONH$
80	Me	Et	$cis\text{-}3,5\text{-di-}CH_3\text{-piperazin-1-yl}CH_2CONH$
81	Me	Et	$Trans\text{-}2,6\text{-di-}CH_3\text{-piperazin-1-yl}CH_2CONH$
82	Me	Et	$Trans\text{-}3,5\text{-di-}CH_3\text{-piperazin-1-yl}CH_2CONH$
83	Me	Et	$(R)\text{-}1\text{-Ethylpyrrolidin-2-yl}CH_2NHCONH$
84	Me	Et	$(S)\text{-}1\text{-Ethylpyrrolidin-2-yl}CH_2NHCONH$
85	Me	Et	$5\text{-}CH_3\text{-pyrazin-2-yl}CH_2NHCH_2CONH$

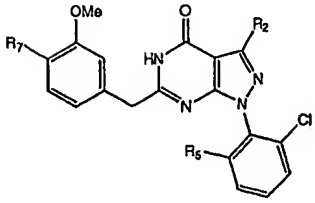
Table XXV



(a)



(b)



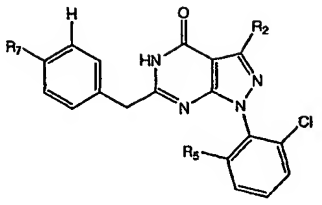
(c)

Ex. #	R^5	R^2	R^7
1	Me	cyc-Pr	1-CH_3-piperazin-4-ylCH_2CONH
2	Me	cyc-Pr	$CH_3NHCONH$
3	Me	cyc-Pr	Morpholin-4-ylCH_2CONH
4	Me	cyc-Pr	Azetidin-1-ylCH_2CONH
5	Me	cyc-Pr	$(CH_3)_2NCH_2CH_2SO_2NH$
6	Me	cyc-Pr	$EtO_2CCH_2NHCONH$
7	Me	cyc-Pr	Hydantoin-1-yl
8	Me	cyc-Pr	$HOCH_2CH_2NHCONH$
9	Me	cyc-Pr	$HO_2C(CH_2)_2CONH$
10	Me	cyc-Pr	Imidazol-1-ylCH_2CONH
11	Me	cyc-Pr	Morpholin-4-yl$CH_2CH_2NHCSNH$
12	Me	cyc-Pr	$HO_2CCH_2NHCONH$
13	Me	cyc-Pr	$HO_2C(CH_2)_3CONH$
14	Me	cyc-Pr	H_2NCH_2CONH
15	Me	cyc-Pr	CH_3NHCH_2CONH
16	Me	cyc-Pr	4-F-phenylCH_2NHCH_2CONH
17	Me	cyc-Pr	Pyrrolidin-1-ylCH_2CONH
18	Me	cyc-Pr	pyrid-2-ylCH_2NHCH_2CONH
19	Me	cyc-Pr	pyrid-3-ylCH_2NHCH_2CONH
20	Me	cyc-Pr	pyrid-4-ylCH_2NHCH_2CONH
21	Me	cyc-Pr	$BocNHCH_2CH_2NHCH_2CONH$
22	Me	cyc-Pr	$HOCH_2CH(CH_3)NHCH_2CONH$
23	Me	cyc-Pr	$CH_3CH(OH)CH_2NHCH_2CONH$
24	Me	cyc-Pr	$H_2NCH_2CH_2NHCH_2CONH$
25	Me	cyc-Pr	Morpholin-4-yl$CH_2CH_2NHCH_2CONH$
26	Me	cyc-Pr	1-CH_3-piperidin-4-yl$N(CH_3)CH_2CONH$
27	Me	cyc-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$

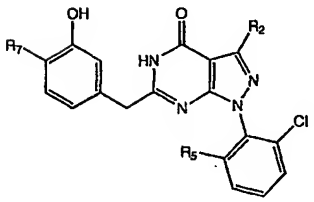
28	Me	cyc-Pr	$(CH_3)_2NCH(CH_3)CONH$
29	Me	cyc-Pr	$1\text{-}CH_3\text{-}L\text{-}prolylNH$
30	Me	cyc-Pr	$Homopiperazin\text{-}1\text{-}ylCH_2CONH$
31	Me	cyc-Pr	$CH_3CH_2NHCH_2CONH$
32	Me	cyc-Pr	$4\text{-}(CH_2NH_2)piperidin\text{-}1\text{-}ylCH_2CONH$
33	Me	cyc-Pr	$(CH_3)_2NCH_2CH_2NHCH_2CONH$
34	Me	cyc-Pr	*cyclo*-$C_3H_5NHCH_2CONH$
35	Me	cyc-Pr	$Piperidin\text{-}4\text{-}ylCH_2NHCH_2CONH$
36	Me	cyc-Pr	$HO(CH_2)_3NHCH_2CONH$
37	Me	cyc-Pr	$1\text{-}Bocpiperidin\text{-}4\text{-}ylCH_2NHCH_2CONH$
38	Me	cyc-Pr	$HOCH_2CH_2NHCH_2CONH$
39	Me	cyc-Pr	*cyclo*-$C_4H_7NHCH_2CONH$
40	Me	cyc-Pr	$Azetidin\text{-}3\text{-}ylCONH$
41	Me	cyc-Pr	$D\text{-}prolylNH\cdot HCl$
42	Me	cyc-Pr	$Boc\text{-}D\text{-}prolylNH$
43	Me	cyc-Pr	$L\text{-}prolylNH\cdot HCl$
44	Me	cyc-Pr	$Boc\text{-}L\text{-}prolylNH$
45	Me	cyc-Pr	$Piperidin\text{-}1\text{-}ylCH_2CH_2NHCH_2CONH$
46	Me	cyc-Pr	$(CH_3)_2CHNHCH_2CONH$
47	Me	cyc-Pr	$BocNHCH_2CH_2CONH$
48	Me	cyc-Pr	$Piperazin\text{-}2\text{-}yl\text{-}CONH$
49	Me	cyc-Pr	$4\text{-}Me\text{-}piperazin\text{-}2\text{-}yl\text{-}CONH$
50	Me	cyc-Pr	$Piperidin\text{-}1\text{-}ylNHCONH$
51	Me	cyc-Pr	$H_2NCH_2CH_2NHCONH\cdot F_3CCO_2H$
52	Me	cyc-Pr	$pyrid\text{-}2\text{-}ylNHCONH$
53	Me	cyc-Pr	$(CH_3)_2NCH_2CH_2NHCONH$
54	Me	cyc-Pr	$BocNHCH_2CH_2NHCONH$
55	Me	cyc-Pr	$HO(CH_2)_4NHCONH$
56	Me	cyc-Pr	$(CH_3)_2NNHCONH$
57	Me	cyc-Pr	$(CH_3)_2N(CH_2)_3NHCONH$
58	Me	cyc-Pr	$1\text{-}CH_3\text{-}homopiperazin\text{-}4\text{-}yl\text{-}CONH$
59	Me	cyc-Pr	$CH_3SO_2NHCONH$
60	Me	cyc-Pr	$CH_3ONHCONH$
61	Me	cyc-Pr	$(CH_3)_2NCH_2CH_2NHCONH$
62	Me	cyc-Pr	$1\text{-}CH_3\text{-}piperidin\text{-}4\text{-}ylN(CH_3)CONH$
63	Me	cyc-Pr	$Tetrahydrofur\text{-}2\text{-}ylCH_2NHCONH$
64	Me	cyc-Pr	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$

65	Me	cyc-Pr	$HOCH_2CH(CH_3)NHCONH$
66	Me	cyc-Pr	$CH_3CH(OH)CH_2NHCONH$
67	Me	cyc-Pr	$HOCH_2CH_2NHCONH$
68	Me	cyc-Pr	Morpholin-4-ylNHCONH
69	Me	cyc-Pr	$(CH_3)_2NCH(CH_3)CH_2NHCONH$
70	Me	cyc-Pr	$1\text{-}CH_3$-piperazin-4-ylNHCONH
71	Me	cyc-Pr	Morpholin-4-yl$CH_2CH_2NHCONH$
72	Me	cyc-Pr	$1\text{-}CH_3$-piperazin-4-ylCONH
73	Me	cyc-Pr	pyrid-2-ylNHCONH
74	Me	cyc-Pr	pyrid-4-ylNHCONH
75	Me	cyc-Pr	Pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$
76	Me	cyc-Pr	$2\text{-}CH_3$-piperazin-1-ylCONH
77	Me	cyc-Pr	$3\text{-}CH_3$-piperazin-1-ylCH_2CONH
78	Me	cyc-Pr	trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH
79	Me	cyc-Pr	cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH
80	Me	cyc-Pr	cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH
81	Me	cyc-Pr	trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH
82	Me	cyc-Pr	trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH
83	Me	cyc-Pr	(R)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
84	Me	cyc-Pr	(S)-1-Ethylpyrrolidin-2-yl$CH_2NHCONH$
85	Me	cyc-Pr	$5\text{-}CH_3$-pyrazin-2-ylCH_2NHCH_2CONH

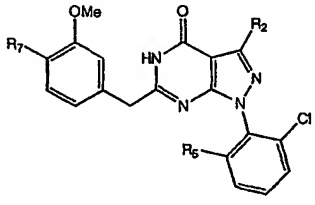
Table XXVI



(a)



(b)



(c)

Ex.#	R^5	R^2	R^7
1	Me	i-Pr	$1\text{-}CH_3$-piperazin-4-ylCH_2CONH
2	Me	i-Pr	$CH_3NHCONH$
3	Me	i-Pr	Morpholin-4-ylCH_2CONH
4	Me	i-Pr	Azetidin-1-ylCH_2CONH

5	Me	i-Pr	$(CH_3)_2NCH_2CH_2SO_2NH$
6	Me	i-Pr	$EtO_2CCH_2NHCONH$
7	Me	i-Pr	Hydantoin-1-yl
8	Me	i-Pr	$HOCH_2CH_2NHCONH$
9	Me	i-Pr	$HO_2C(CH_2)_2CONH$
10	Me	i-Pr	Imidazol-1-ylCH_2CONH
11	Me	i-Pr	Morpholin-4-yl$CH_2CH_2NHCSNH$
12	Me	i-Pr	$HO_2CCH_2NHCONH$
13	Me	i-Pr	$HO_2C(CH_2)_3CONH$
14	Me	i-Pr	H_2NCH_2CONH
15	Me	i-Pr	CH_3NHCH_2CONH
16	Me	i-Pr	4-F-phenylCH_2NHCH_2CONH
17	Me	i-Pr	Pyrrolidin-1-ylCH_2CONH
18	Me	i-Pr	Pyrid-2-ylCH_2NHCH_2CONH
19	Me	i-Pr	Pyrid-3-ylCH_2NHCH_2CONH
20	Me	i-Pr	Pyrid-4-ylCH_2NHCH_2CONH
21	Me	i-Pr	$BocNHCH_2CH_2NHCH_2CONH$
22	Me	i-Pr	$HOCH_2CH(CH_3)NHCH_2CONH$
23	Me	i-Pr	$CH_3CH(OH)CH_2NHCH_2CONH$
24	Me	i-Pr	$H_2NCH_2CH_2NHCH_2CONH$
25	Me	i-Pr	Morpholin-4-yl$CH_2CH_2NHCH_2CONH$
26	Me	i-Pr	1-CH_3-piperidin-4-yl$N(CH_3)CH_2CONH$
27	Me	i-Pr	$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CONH$
28	Me	i-Pr	$(CH_3)_2NCH(CH_3)CONH$
29	Me	i-Pr	1-CH_3-L-prolylNH
30	Me	i-Pr	Homopiperazin-1-ylCH_2CONH
31	Me	i-Pr	$CH_3CH_2NHCH_2CONH$
32	Me	i-Pr	4-(CH_2NH_2)piperidin-1-ylCH_2CONH
33	Me	i-Pr	$(CH_3)_2NCH_2CH_2NHCH_2CONH$
34	Me	i-Pr	*Cyclo*-$C_3H_5NHCH_2CONH$
35	Me	i-Pr	Piperidin-4-ylCH_2NHCH_2CONH
36	Me	i-Pr	$HO(CH_2)_3NHCH_2CONH$
37	Me	i-Pr	1-Bocpiperidin-4-ylCH_2NHCH_2CONH
38	Me	i-Pr	$HOCH_2CH_2NHCH_2CONH$
39	Me	i-Pr	*Cyclo*-$C_4H_7NHCH_2CONH$
40	Me	i-Pr	Azetidin-3-ylCONH
41	Me	i-Pr	D-prolylNH·HCl

42	Me	i-Pr	Boc-D-prolylNH
43	Me	i-Pr	L-prolylNH·HCl
44	Me	i-Pr	Boc-L-prolylNH
45	Me	i-Pr	Piperidin-1-yl$CH_2CH_2NHCH_2CONH$
46	Me	i-Pr	$(CH_3)_2CHNHCH_2CONH$
47	Me	i-Pr	$BocNHCH_2CH_2CONH$
48	Me	i-Pr	Piperazin-2-yl-CONH
49	Me	i-Pr	4-Me-piperazin-2-yl-CONH
50	Me	i-Pr	Piperidin-1-ylNHCONH
51	Me	i-Pr	$H_2NCH_2CH_2NHCONH \cdot F_3CCO_2H$
52	Me	i-Pr	Pyrid-2-ylNHCONH
53	Me	i-Pr	$(CH_3)_2NCH_2CH_2NHCONH$
54	Me	i-Pr	$BocNHCH_2CH_2NHCONH$
55	Me	i-Pr	$HO(CH_2)_4NHCONH$
56	Me	i-Pr	$(CH_3)_2NNHCONH$
57	Me	i-Pr	$(CH_3)_2N(CH_2)_3NHCONH$
58	Me	i-Pr	1-CH_3-homopiperazin-4-yl-CONH
59	Me	i-Pr	$CH_3SO_2NHCONH$
60	Me	i-Pr	$CH_3ONHCONH$
61	Me	i-Pr	$(CH_3)_2NCH_2CH_2NHCONH$
62	Me	i-Pr	1-CH_3-piperidin-4-ylN(CH_3)CONH
63	Me	i-Pr	Tetrahydrofur-2-yl$CH_2NHCONH$
64	Me	i-Pr	$CH_3(CH_2)_2CH(OH)CH_2NHCONH$
65	Me	i-Pr	$HOCH_2CH(CH_3)NHCONH$
66	Me	i-Pr	$CH_3CH(OH)CH_2NHCONH$
67	Me	i-Pr	$HOCH_2CH_2NHCONH$
68	Me	i-Pr	Morpholin-4-ylNHCONH
69	Me	i-Pr	$(CH_3)_2NCH(CH_3)CH_2NHCONH$
70	Me	i-Pr	1-CH_3-piperazin-4-ylNHCONH
71	Me	i-Pr	Morpholin-4-yl$CH_2CH_2NHCONH$
72	Me	i-Pr	1-CH_3-piperazin-4-ylCONH
73	Me	i-Pr	Pyrid-2-ylNHCONH
74	Me	i-Pr	Pyrid-4-ylNHCONH
75	Me	i-Pr	Pyrrolidin-1-yl$CH_2CH_2NHCH_2CONH$
76	Me	i-Pr	2-CH_3-piperazin-1-ylCONH
77	Me	i-Pr	3-CH_3-piperazin-1-ylCH_2CONH
78	Me	i-Pr	Trans-2,5-di-CH_3-piperazin-1-ylCH_2CONH

79	Me	i-Pr	Cis-2,6-di-CH_3-piperazin-1-ylCH_2CONH
80	Me	i-Pr	Cis-3,5-di-CH_3-piperazin-1-ylCH_2CONH
81	Me	i-Pr	Trans-2,6-di-CH_3-piperazin-1-ylCH_2CONH
82	Me	i-Pr	Trans-3,5-di-CH_3-piperazin-1-ylCH_2CONH
83	Me	i-Pr	(R)-1-Ethylpyrrolidin-2-ylCH_2NHCONH
84	Me	i-Pr	(S)-1-Ethylpyrrolidin-2-ylCH_2NHCONH
85	Me	i-Pr	5-CH_3-pyrazin-2-ylCH_2NHCH_2CONH

UTILITY

The present invention provides a method of treating cancer or other proliferative diseases comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of formula (I) or (II), or a pharmaceutically acceptable salt form thereof.

The present invention also provides a novel method of treating cancer or other proliferative diseases comprising administering to a host in need of such treatment a therapeutically effective amount of:

(a) a compound of formula (I) or (II), or a pharmaceutically acceptable salt form thereof; and,

(b) at least one compound selected from the group consisting of anti-cancer agents and anti-proliferative agents.

Selected species were selective for their activity against cyclin dependent kinases and their cyclin bound complexes and were less active against other known serine/threonine kinases such as Protein Kinase A (PKA) and Protein Kinase C (PKC). In addition, these inhibitors were less active against tyrosine kinases such as c-Abl.

Inhibition of Kinase/Cyclin Complex Enzymatic Activity

Several of the compounds disclosed in this invention were assayed for their inhibitory activity against cyclin dependent kinase4/D1, cyclin dependent kinase1/B kinase, cyclin dependent kinase2/A kinase, and cyclin dependent kinase2/E kinase complexes. Briefly, the *in vitro* assays

employ cell lysates from insect cells expressing either of the kinases and subsequently their corresponding regulatory units. The cyclin dependent kinase2/cyclinE is purified from insect cells expressing His-tagged cyclin dependent kinase 2 and cyclin E. The cyclin dependent kinase/cyclin lysate is combined in a microtitre-type plate along with a kinase compatible buffer, ^{32}P-labeled ATP at a concentration of 50 mM, a GST-Rb fusion protein and the test compound at varying concentrations. The kinase reaction is allowed to proceeded with the radiolabled ATP, then effectively stopped by the addition of a large excess of EDTA and unlabeled ATP. The GST-Rb labeled protein is sequestered on a GSH-Sepharose bead suspension, washed, resuspended in scintillant, and the ^{32}P activity detected in a scintillation counter. The compound concentration which inhibits 50% of the kinase activity was calculated for each compound. A compound was considered active if its IC_{50} was found to be less than 1 μM.

Inhibition of HCT 116 Cancer Cell Proliferation

To test the cellular activity of several compounds disclosed in this invention, we examined the effect of these compounds on cultured HCT116 cells and determined their effect on cell-cycle progression by the colorimetric cytotoxcity test using sulforhodamine B (Skehan et al. *J. Natl. Cancer Inst.* 82:1107-12, 1990). Briefly, HCT116 cells are cultured in the presence of test compounds at increasing concentrations. At selected time points, groups of cells are fixed with trichloroacetic acid and stained with sulforhodamine B (SRB). Unbound dye was removed by washing and protein-bound dye was extracted for determination of optical density. A compound was considered active if its IC_{50} was found to be less than 10 μM.

All patents, patent applications and other applicable publications mentioned herein, are

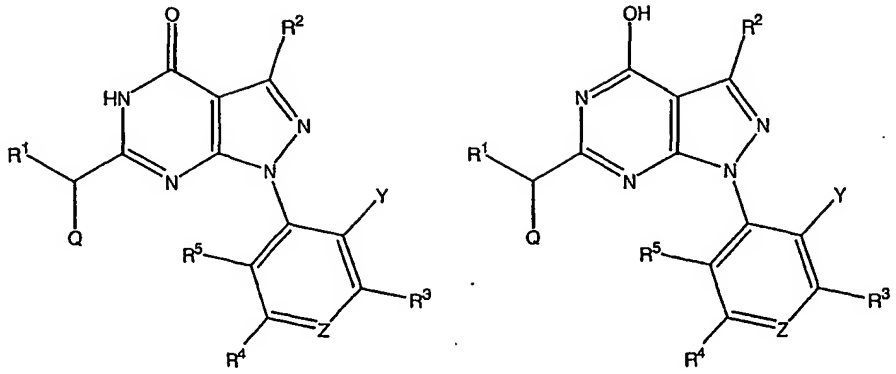
incorporated by reference as though set forth in full in this specification.

The scope of the following claims is intended to encompas all obvious chnages in the details, materials, and arrangement of steps that will occur to one of ordinary skill in the art.

CLAIMS

What is claimed is:

1. A compound of formula (I) or its tautomer, formula (II):



(I) (II)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

Q is selected from the group consisting of: H, OH, and C_{1-7} alkyl;

Y is selected from the group consisting of: F, Cl, Br, and I;

Z is selected from the group consisting of: N, C-H, C-F, C-Cl, C-Br, C-I, C-CF_3, C-NO_2, C-C_{1-4} alkyl optionally containing from 1-8 substitution groups, C-C_{2-4} alkenyl optionally containing from 1-8 substitution groups, C-C_{2-4} alkynyl optionally containing from 1-8 substitution groups, C-C_{1-4} alkoxy optionally containing from 1-8 substitution groups, C-CO_2H, C-CHO, C-$CONR^6R^9$, C-CO_2C_{1-3} alkyl, C-$C(O)C_{1-2}$ alkyl, C-CH_2NHR^6, C-$CONR^6NR^6R^9$, C-NR^6R^9; C-$SO_2NR^6R^9$, C-CR=NNR^6R^9, C-CR^6=NOR^6, and C-R^6;

R^1 is selected from the group consisting of aryl and 5-10 membered aromatic heterocycle containing from 1-4 heteroatoms selected from O, N, and S, and wherein the aryl or the 5-10 membered aromatic heterocycle is optionally substituted with 1-5 R^7 groups;

R^2 is selected from the group consisting of: C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, S-C_{1-3} alkyl, O-C_{1-3} alkyl, NH_2, NH-C_{1-3} alkyl, N(C_{1-2} alkyl)$_2$, OCF_3, cyclopropyl optionally containing from 1-4 substitution groups, cyclobutyl, cyclopropylmethyl, cyclobutylmethyl, 1-methylcyclopropyl, 1-methylcyclobutyl, CH_2CN, CH_2OH, CH_2OCH_3, CH_2NH_2, CH_2NHC_{1-3} alkyl, CH_2NMe_2, CF_3, CHO, OCH_2CH_2OH, OCH(Me)CH_2OH, OCH_2CH(Me)OH, $OCH_2CH_2NMe_2$, and CHF_2;

R^3 is selected from the group consisting of: H, F, Cl, Br, I, CF_3, CHO, CHR^6OH, $COCF_3$, CH=NOH, $CH=NOCH_3$, $CH=NNH_2$, CH=NNHMe, $CH=NNMe_2$, $CH=CHR^6$, C_{1-3} alkyl, C_{1-3} alkoxy, CO_2H, $CONH_2$, CONH(C_{1-3} alkyl), $CONR^6R^9$, CO_2C_{1-3} alkyl, C(O)C_{1-2} alkyl, NH_2, NHR^6, and NR^6R^9;

R^4 is selected from the group consisting of: H, F, Cl, Br, I, CF_3, C_{1-3} alkyl, C_{2-3} alkenyl, NH_2, NHR^6, and NR^6R^9;

R^5 is selected from the group consisting of: H, C_{1-3} alkyl, F, Cl, Br, I, CF_3, and C_{2-3} alkenyl;

R^6 and R^9 are independently, at each occurrence, the same or different, and are selected from the group consisting of: H, C_{1-8} alkyl optionally containing from 1-8 substitution groups, and C_{3-7} cyclo-alkyl;

alternatively, R^6 and R^9, together with the atoms to which they are attached, form a heterocycle having 5-7 atoms in the ring and containing 0-1 additional N,

O, or S atom; or, R^6 and R^9, together with the atoms to which they are attached, form a bicyclic heterocycle having 9-11 atoms in the ring and containing one additional N, S, or O atom; or, R^6 and R^9, together with the atoms to which they are attached, form a 5-7 membered ring and containing 0-3 additional N, S, or O atoms;

R^7 is independently, at each occurrence, selected from the group consisting of: OH, C_{1-6} alkoxy, OC_{2-6} alkyl-CO_2H, O-C_{2-6}-alkyl-NR^6R^9, F, Cl, Br, I, CF_3, OCF_3, -CN, $-NO_2$, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^6R^9$, $NR^6CONHOR^6$, $NR^6CONHSO_2R^6$, $NHNR^6C(O)OR^6$, $NR^6C(O)NR^6R^9$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $-SO_2NR^6R^9$, $NHSO_2NHCO_2C_{1-4}$ alkyl, $NR^6SO_2NR^6R^9$, $NR^6SO_2CHR^6CH_2NR^6R^9$, $NR^6COCHR^6NR^6R^9$, $NR^6COCHR^6NR^6CHR^6R^9$, $NR^6COCH_2CHR^6NR^6R^9$, $NR^6COCHR^6CH_2NR^6R^9$, $NR^6CO(CH_2)_mNR^6R^9$, $NR^6CONR^6(CH_2)_nNR^6R^9$, $NR^6CO_2(CHR^6)_nNR^6R^9$, $CONR^6NR^6R^9$, $NR^6CONR^6NR^6R^9$, C_{3-10} carbocycle, $NHCONR^6$, $NHCONHCH_2R^6$, $NHCOR^6$, $NHCOCH_2R^6$, C_{1-10} alkyl optionally substituted with 1-5 substitution groups, C_{2-10} alkenyl optionally substituted with 1-5 substitution groups, C_{2-10} alkynyl optionally substituted with 1-5 substitution groups, and C_{3-10} heterocycle containing 1-4 heteroatoms selected from O, N, and S;

R^8 is independently, at each occurrence, selected from the group consisting of: =O, OH, C_{3-6} cycloalkyl, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, F, Cl, Br, I, CO_2H, COR^6, CO_2(benzyl), $CO_2(C_{1-6}$ alkyl), and $CONR^6R^9$;

n at each occurrence is independently selected from 2, 3, 4, 5, and 6; and,

m at each occurrence is independently selected from 3, 4, 5, and 6.

2. A compound according to claim 1, wherein:

Q is selected from the group: H, OH, and CH_3;

Y is selected from the group: F, Cl, and Br;

Z is selected from the group consisting of: N, CH, CF, CCl, CBr, CI, C-CF_3, C-NO_2, C-C_{1-4} alkyl optionally substituted with 1-5 substitution groups, C-C_{2-4} alkenyl optionally substituted with 1-5 substitution groups, C-C_{2-4} alkynyl optionally substituted with 1-5 substitution groups, C-C_{1-4} alkoxy, C-CO_2H, C-CHO, C-$CONR^6R^9$, C-CO_2C_{1-3} alkyl, C-$C(O)C_{1-2}$ alkyl, C-CH_2NHR^6, C-$CONR^6NR^6R^9$, C-NR^6R^9; C-$SO_2NR^6R^9$, C-$CR=NNR^6R^9$, C-$CR^6=NOR^6$, and C-R^6;

R^1 is selected from the group: phenyl and a 5-10 membered aromatic heterocycle containing from 1-4 heteroatoms selected from O, N, and S, and R^1 is substituted with 0-3 R^7;

R^2 is selected from the group: C_{2-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, S-C_{1-2} alkyl, O-C_{1-2} alkyl, cyclopropyl, cyclobutyl, 1-methylcyclopropyl, CH_2CN, CH_2OH, CH_2OCH_3, CH_2NH_2, CH_2NMe_2, CF_3, and CHO;

R^3 is independently selected from the group: H, F, Cl, CH_3, CH_2CH_3, CHO, CHR^9OH, $COCF_3$, CH=NOH, $CH=NOCH_3$, $CH=NNH_2$, CH=NNHMe, $CH=NNMe_2$, and $CH=CHR^8$;

R^4 is independently selected from the group: H, F, Cl, and CH_3;

R^5 is independently selected from the group: H, CH_3, F, Cl, Br, and CF_3;

R^6 and R^9 are the same or different, and are selected from the group consisting of H, C_{1-8} optionally substituted with 1-5 substitution groups, and cyclo-alkyl C_{3-7};

alternatively, R^6 and R^9, together with the atoms to which they are attached, form a heterocycle having 5-7 atoms in the ring and containing 0-1 additional N, O, or S atom or, form a bicyclic heterocycle having 9-11 atoms in the ring and containing one additional N, S, or O atom or, form a 5-7 membered ring and containing 0-3 additional N, S, or O atoms;

R^7 is independently, at each occurrence, selected from the group consisting of: OH, C_{1-6} alkoxy, OC_{2-6} alkyl-CO_2H, O-C_{2-6}-alkyl-NR^6R^9, F, Cl, Br, I, CF_3, OCF_3, -CN, $-NO_2$, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^6R^9$, $NR^6CONHOR^6$, $NR^6CONHSO_2R^6$, $NHNR^6C(O)OR^6$, $NR^6C(O)NR^6R^9$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $-SO_2NR^6R^9$, $NHSO_2NHCO_2C_{1-4}$ alkyl, $NR^6SO_2NR^6R^9$, $NR^6SO_2CHR^6CH_2NR^6R^9$, $NR^6COCHR^6NR^6R^9$, $NR^6COCHR^6NR^6CHR^6R^9$, $NR^6COCH_2CHR^6NR^6R^9$, $NR^6COCHR^6CH_2NR^6R^9$, $NR^6CO(CH_2)_mNR^6R^9$, $NR^6CONR^6(CH_2)_nNR^6R^9$, $NR^6CO_2(CHR^6)_nNR^6R^9$, $CONR^6NR^6R^9$, $NR^6CONR^6NR^6R^9$, C_{3-10} carbocycle, $NHCONR^6$, $NHCONHCH_2R^6$, $NHCOR^6$, $NHCOCH_2R^6$, C_{1-10} alkyl optionally substituted with 0, 1, 2 or 3 R^8 groups, C_{2-10} alkenyl optionally substituted with 0, 1, 2 or 3 R^8 groups, C_{2-10} alkynyl optionally substituted with 0, 1, 2, or 3 R^8 groups, and C_{3-10} heterocycle containing 1-4 heteroatoms selected from O, N, and S;

R^8 is independently, at each occurrence, selected from the group: =O, OH, C_{3-6} cycloalkyl, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, F, Cl, Br, I, CO_2H, COR^6, CO_2(benzyl), $CO_2(C_{1-6}$ alkyl), and $CONR^6R^9$;

n at each occurrence is independently selected from 2, 3, 4, 5, and 6; and,

m at each occurrence is independently selected from 3, 4, 5, and 6.

3. A compound according to claim 2, wherein: R^2 is selected from the group consisting of: ethyl, cyclopropyl, cyclobutyl, 1-methylcyclopropyl, and CF_3.

4. A compound accordoing to claim 3 wherein:

R^5 is CH_3.

5. A compound according to claim 1, wherein the compound is selected from the group consisting of:

a) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-hydroxy-3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

b) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

c) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-hydroxy-4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

d) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

e) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

f) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

g) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-acetamidobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

h) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(*N*-(*t*-butoxycarbonyl)glycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

i) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(2-(*N*,*N*-dimethylamino)ethylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

j) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-amino-2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

k) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(pyrid-2-ylmethylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

l) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-glycinamidobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

m) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(pyrid-4-ylmethylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

n) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(*para*-biphen-4-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

o) 1-(2,6-dichlorophenyl)-3-ethyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

p) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(4-methylpiperazin-1-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

q) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(dimethylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

r) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(2-(hydroxymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

s) 1-(2,6-dichlorophenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

t) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(methoxyaminocarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

u) 1-(2,6-dichlorophenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

v) 1-(2,6-dichlorophenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

w) 1-(2-chloro-6-methylphenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

x) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3,5-dihydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

y) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-hydroxy-3-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

z) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-amino-3-nitrobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

aa) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(methylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ab) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-(methane sulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ac) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(methane sulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ad) 1-(2,6-dichloro-4-(pyrid-3-ylaminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ae) 1-(2,6-dichloro-4-(pyrid-4-ylaminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

af) 1-(2,6-dichloro-4-(cyclopropylaminocarbonyl) phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d] pyrimidin-4-one;

ag) 1-(2,6-dichloro-4-(*N*-(pyrid-3-ylmethyl) aminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl) pyrazolo[3,4-d]pyrimidin-4-one;

ah) 1-(2,6-dichloro-4-(*N*-(pyrid-2-ylmethyl) aminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl) pyrazolo[3,4-d]pyrimidin-4-one;

ai) 1-(2,6-dichloro-4-(ethylaminocarbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

aj) 1-(2,6-dichloro-4-(benzylaminocarbonyl)phenyl)-3-ethyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ak) 1-(2,6-dichloro-4-(2-(dimethylamino)ethylamino carbonyl)phenyl)-3-ethyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

al) 1-(2,6-dichloro-4-(methylaminocarbonyl)phenyl)-3-ethyl-6-(4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

am) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(3-(*N*,*N*-dimethylglycinamido)-2-methylbenzyl)pyrazolo[3,4-d] pyrimidin-4-one;

an) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(*N*,*N*-dimethyl glycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ao) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(*N*-methylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ap) 1-(2,6-dichloro-4-bromophenyl)-3-ethyl-6-(4-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

aq) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methoxycarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ar) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

as) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-hydroxy-4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

at) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

au) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(methane sulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

av) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(difluoroacetamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

aw) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(acetamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ax) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(methylaminocarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

ay) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

az) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(azetidin-3-ylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

ba) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-aminoethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

bb) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(isopropylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

bc) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-fluorobenzylaminomethylcarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

bd) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(pyrrolidin-1-ylmethylcarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

be) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(pyrid-2-ylmethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

bf) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(*t*-butoxycarbonylamino)ethylaminomethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

bg) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(pyrid-3-ylmethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

bh) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(pyrid-4-ylmethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

bi) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(morpholin-4-yl)ethylaminomethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

bj) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(methylaminocarbonylmethyl)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

bk) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(ethylaminocarbonylmethyl)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

bl) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(piperazin-1-ylcarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bm) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-methylpyrid-3-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

bn) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethylaminocarbonylmethyl)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

bo) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2,2-dimethylhydrazin-1-ylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

bp) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1-hydroxybut-4-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

bq) (+/-)1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-hydroxyprop-1-ylaminomethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

br) (+/-)1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1-hydroxyprop-2-ylaminomethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

bs) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(pyrid-3-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

bt) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bu) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(dimethylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bv) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(pyrid-4-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

bw) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*,*N*-dimethylglycinamido)-3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bx) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*,*N*-dimethylglycinamido)-3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

by) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methylaminocarbonylamino)-3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

bz) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-(3-(dimethylamino)propyl)aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ca) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(benzoxazol-2-on-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

cb) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylcarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cc) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl, *N*-(2-(dimethylamino)ethyl)aminocarbonylmethyl)benzyl)-pyrazolo[3,4-d]pyrimidin-4-one;

cd) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methylaminocarbonylamino)-3-hydroxybenzyl)pyrazolo [3,4-d]pyrimidin-4-one;

ce) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylmethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

cf) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(piperazin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

cg) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(morpholin-4-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

ch) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(imidazol-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

ci) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)aminomethylcarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cj) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(cyclopropylaminomethylcarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

ck) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*,*N*-dimethylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cl) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cm) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-aminoindazol-5-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

cn) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl,*N*-(2-(dimethylamino)ethyl)aminomethylcarbonyl amino)benzyl)-pyrazolo[3,4-d]pyrimidin-4-one;

co) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylcarbonylmethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cp) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(azetidin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cq) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-hydroxy-4-(imidazol-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cr) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cs) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(3-(dimethylamino)prop-1-ylaminocarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

ct) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylhomopiperazin-1-ylcarbonylamino)benzyl)pyrazolo [3,4-d]pyrimidin-4-one;

cu) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-2-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cv) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*t*-butoxycarbonylaminosulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cw) 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cx) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(morpholin-4-yl)ethylaminothiocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cy) 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-(*N*,*N*-dimethylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

cz) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-bromobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

da) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(piperazin-2-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

db) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1,4-dimethylpiperazin-2-ylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dc) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethylsulfonamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dd) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-amino-3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

de) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-hydantoin-3-ylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

df) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(2H-1,4-benz oxazin-3-on-7-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

dg) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-(2-(dimethylamino)ethyl)aminocarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

dh) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-hydroxyethylaminocarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

di) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dj) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dk) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-glycinamidobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dl) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dm) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)ethylaminomethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

dn) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-(aminomethyl)piperidin-1-ylmethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

do) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(homopiperazin-1-ylmethylcarbonylamino)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

dp) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(ethylaminomethylcarbonylamino)benzyl)pyrazolo[3,4-d] pyrimidin-4-one;

dq) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(dimethylaminomethyl)-3-hydroxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dr) (*S*)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methylprolinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ds) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-,*N*-dimethylalaninamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dt) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1,4,7-triazacyclonon-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

du) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-amino-2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dv) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(morpholin-4-yl)ethylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dw) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(*N*-,*N*-dimethylglycinamido)-2-methylbenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dx) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dy) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(morpholin-4-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

dz) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methoxyaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ea) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methanesulfonamidocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

eb) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl,*N*-(2-(dimethylamino)ethyl)aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ec) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl,*N*-(1-methylpiperidin-4-yl)aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ed) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(tetrahydrofur-2-ylmethylaminocarbonylamino)benzyl)-pyrazolo[3,4-d]pyrimidin-4-one;

ee) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1-hydroxypent-2-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ef) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(1-hydroxyprop-2-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

eg) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-hydroxyprop-1-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

eh) (+/-)-1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-(dimethylamino)prop-1-ylaminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ei) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(3-hydroxy-4-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ej) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(indazol-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

ek) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(indazol-5-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

el) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(indazol-4-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

em) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(benzoxazol-2-on-5-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-one;

en) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(3-hydroxy-4-nitrobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

eo) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(4-aminobenzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ep) 1-(2,4,6-trichlorophenyl)-3-cyclopropyl-6-(4-(*N,N*-dimethylglycinamido)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

eq) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*cis*-3,4-dimethylpiperazin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

er) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*trans*-2,5-dimethylpiperazin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

es) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(3-methylpiperazin-1-ylmethylcarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

et) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(5-(dimethylaminomethyl)-1-methylpyrrol-2-yl)pyrazolo[3,4-d]pyrimidin-4-one;

eu) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(4-methylpiperazin-1-ylaminocarbony)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ev) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(*N*-methyl, *N*-(2-(dimethylamino)ethyl)aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ew) 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-(*N*-methyl,*N*-(1-methylpiperidin-4-yl)aminocarbonylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ex) 1-(2-chloro-6-methylphenyl)-3-isopropyl-6-(4-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)aminomethylcarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ey) 1-(2,4,6-trichlorophenyl)-3-ethyl-6-(4-(*N*-methyl,*N*-((3S, 4S)-4-dimethylaminotetrahydrofur-3-yl)aminocarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ez) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(3-(*N*-methyl, *N*-(2-(dimethylamino)ethyl)aminocarbonyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fa) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(2-pyrrolidin-1-ylethylaminocarbonyamino)benzyl)pyrazolo [3,4-d] pyrimidin-4-one;

fb) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl, *N*-(2-(dimethylamino)ethyl)aminocarbonymethyl)benzyl) pyrazolo[3,4-d]pyrimidin-4-one;

fc) 1-(2,6-dichlorophenyl)-3-isopropyl-6-(4-(*N*-(2-(dimethylamino)ethyl)aminocarbonymethyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fd) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-(2-(dimethylamino)ethyl)aminocarbonyl)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fe) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(methylamino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

ff) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl-*N*-(1-methylpiperidin-4-yl)aminocarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fg) 1-(2,4,6-trichlorophenyl)-3-isopropyl-6-(4-(*N*-methyl, *N*-(2-(dimethylamino)ethyl)aminocarbonyl amino)benzyl)pyrazolo[3,4-d]pyrimidin-4-one;

fh) 1-(2,6-dichloro-4-sulfonamidophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one; and

fi) 1-(4-aminomethyl-2, 6-dichlorophenyl)-3-isopropyl-6-(3-methoxybenzyl)pyrazolo[3,4-d]pyrimidin-4-one.

6. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of any one of claims 1, 2, 3, 4, or 5.

7. A method of inhibiting cyclin dependent kinase enzymatic activity in a patient, comprising: administering to the patient in need of such treatment a therapeutically effective amount of a compound of any one

of claims 1, 2, 3, 4, or 5, or a pharmaceutically acceptable salt form thereof.

8. A method of treating cancer or other proliferative diseases, comprising: administering to a host in need of such treatment a therapeutically effective amount of:

(a) a compound of claim 1-5, or a pharmaceutically acceptable salt form thereof; and,

(b) at least one compound selected from the group consisting of anti-cancer agents and anti-proliferative agents.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 September 2002 (06.09.2002)

PCT

(10) International Publication Number
WO 02/067654 A3

(51) International Patent Classification[7]: C07D 487/04, A61K 31/519

(21) International Application Number: PCT/US02/06002

(22) International Filing Date: 27 February 2002 (27.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/794,825 27 February 2001 (27.02.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

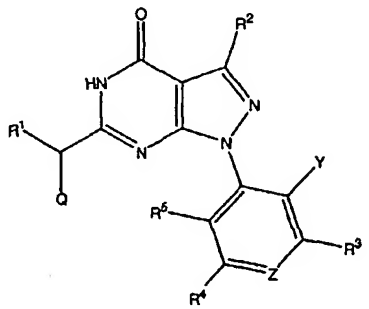
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

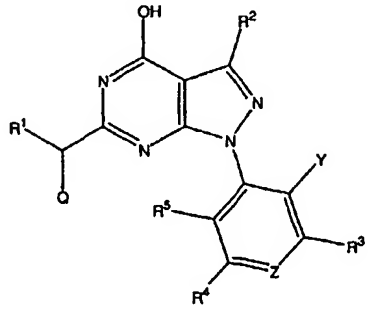
(88) Date of publication of the international search report:
31 October 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 6-SUBSTITUTED PYRAZOLO[3,4-D]PYRIMIDIN-4-ONES USEFUL AS CYCLIN DEPENDENT KINASE INHIBITORS



(I)



(II)

(57) Abstract: The present invention relates to the synthesis of a novel class of pyrazolo[3,4-d]pyrimidin-4-ones of formula (I), alternatively represented by the tautomer (II), that are potent inhibitors of the class of enzymes known as cyclin dependent kinases, which relate to the catalytic subunits cyclin dependent kinase 1-8 and their regulatory subunits know as cyclins A-H, K, N, and T. This invention also provides a novel method of treating cancer or other proliferative diseases by administering a therapeutically effective amount of one of these compounds or a pharmaceutically acceptable salt form thereof. Alternatively, one can treat cancer or other proliferative diseases by administering a therapeutically effective combination of one of the compounds of the present invention and one or more other known anti-cancer or anti-proliferative agents.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/06002

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 487/04; A61K 31/519.
US CL : 544/262; 514/262.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/262; 514/262.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST (IS&R).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/2196 A2 (DU PONT PHARMACEUTICALS COMPANY) 20 April 2000 (20.04.00), page 56, Table III.	1-8
A	EP 0 773 023 A1 (CHEN ET AL) 14 May 1997 (14.05.1997), pages 1-3.	1-8
A	WO 94/13677 A1 (PFIZER INC.) 23 June 1994 (23.06.94), pages 42-45, Preparations G, H, M-Q.	1-8
A	MIYASHIT et. al., Studies On Pyrazolo[3,4-d]Pyrimidine Derivatives. XVIII. Facile Preparation of 1H-Pyrazolo[3,4-d]Pyrimidin-4(5H)-ones. Heterocycles, 1990, Vol 31, No. 7, pages 1309-1314, especially formula 1f on page 1310.	1-8
A	SENGA et. al., Synthesis and Xanthine Oxidase Inhibitory Activity of 4,6-Disubstituted 1-p-Chlorophenylpyrazolo[3,4-d]pyrimidines, Journal of Heterocyclic Chemistry, Nov./Dec.-1982, Vol. 19, No. 6, pages 1565-1567, especially Scheme on page 1565.	1-8

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Date of the actual completion of the international search
22 June 2002 (22.06.2002)

Date of mailing of the international search report
05 SEP 2002

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/06002

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	REDDY et. al., Versatile Synthesis of 6-Alkyl(aryl)-1H-Pyrazolo[3,4-d]pyrimidin-4[5H]-ones, Chemical Abstract No. 174107u, April 1992, Vol. 116, page 860.	1-8